NEW APPLICATIONS OF ORGANOTIN REAGENTS

By

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by

Kelley M. Moran

To Mom and Dad,
with all my love and respect

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Without the support and encouragement of the people around me, I would not be where I am today. In the following paragraphs I would like to thank a few of the many people who have had a positive influence on me as a person and a chemist. First, I would like to thank Shirley Burgess, who introduced me to chemistry during my freshman year in high school. She brought a sense of wonder and a joy of science to her teaching.

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Abstract of Dissertation Presented to the Graduate School
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NEW APPLICATIONS OF ORGANOTIN REAGENTS

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Chairman: Eric J. Enholm
Major Department: Chemistry

Several new applications of organotin reagents have been investigated. Those include a novel free-radical approach to sigmatropic shifts, a new method of elaboration at the β-center of α,β-unsaturated carbonyl compounds, hydroboration of O-stannyl enolates, and the development of a novel polymer bound allylstannane reagent.

It was demonstrated that Claisen rearrangements can be accelerated by the tandem formation of O-stannyl enolates. This unprecedented free-radical mediated approach is as efficient as previous methods, but offers the advantage of mild conditions. A mechanistic investigation was undertaken to ascertain which of two possible mechanisms is most likely taking place. Also, functionalization at two additional reactive sites was successful.

Another project involved elaboration at the β site of α,β-unsaturated carbonyl substrates. An electron deficient allylstannane reagent formed the β-radical site by reaction with enones and also acted as the radical acceptor. This reaction provides the only non-basic and non-nucleophilic alternative to Michael additions to enones.

Conditions for the one-pot transformation of α,β-unsaturated ketones to trans-1,2-diols have been developed. An O-stannyl enolate was formed from an α,β-unsaturated ketone under neutral free-radical conditions. Hydroboration of the electron rich O-stannyl enolate double bond led to the boron intermediate, which after oxidation gave the trans-diol. Cyclic precursors work well; however acyclic precursors led to mono-alcohols.

The synthesis of a non-crosslinked polymer linked allylstannane reagent was investigated. Once completed, this novel new reagent should experience less tin pollution than the crosslinked polymer bound tin-hydride counterparts, as well as faster reaction times.

CHAPTER 1
INTRODUCTION

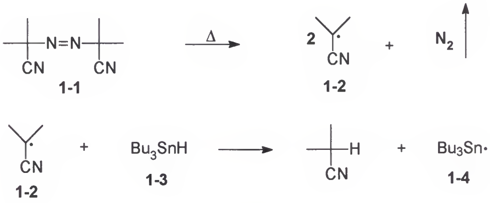
Free-Radical Chemistry

"Free radical" species possess at least one unpaired electron, where the electron is not coordinated with a metal. For carbon centered radicals, the unpaired electron resides in the p-orbital of an sp^2 hybridized central atom. These highly reactive species are formed by homolytic cleavage of a covalent bond. Once formed, free radicals can react with themselves, unlike carbocation and anion reactive intermediates.[1] However, the main utility of the free radical reactive intermediate lies in its reactions with non-radical species such as olefins, carbon-halogen bonds, carbonyls, etc.

Free-radical chemistry has been known for almost one hundred years. Around 1900 Gomberg[2] discovered the stable triphenyl methyl radical and studied its formation and utility. Nearly three decades later, Paneth[3] found that less stable alkyl radicals exist and calculated their lifetimes in the gas phase. The first organic synthesis utilizing free radical intermediates was not accomplished until 1937, when Hey and Waters[4] used benzoyl peroxide, a free radical precursor, to phenylate aromatic species. During the 50s and 60s a deeper understanding of free radical reactions, structure and formation was gained. However, the true scope of free radical organic synthesis was not realized until the 1980s, when key discoveries led to the development of free radical methods for the formation of aliphatic carbon-carbon bonds, the backbone of organic synthesis.[1]

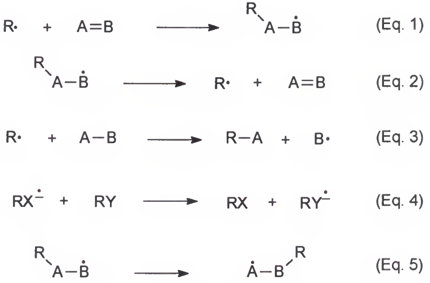
Free radical reactive intermediates were first thought to be too reactive to be of any utility. However, free radical approaches offer many advantages over the more traditional carbocationic and anionic reactions. Reactions with ionic reactive intermediates are heavily influenced by solvation effects and the polarity of surrounding functional groups. Neutral free radical intermediates experience minimal problems with these effects, due to their neutral character. Free radical species also experience less steric hindrance, since the radicals are not coordinated to metals or solvents. Also, basic media, which may destroy surrounding functional groups or epimerize chiral centers, is completely avoided by use of neutral free radical methodology. Therefore, free radical reactions can be conducted in an array of solvents and bulky environments with little or no consequence. Also, when synthesizing chiral compounds or compounds with sensitive functional groups, the approach of choice is always neutral free radical methodology.[5]

In most cases a radical chain mechanism is followed for reactions between a radical and a non-radical species. Two chemical steps, initiation and propagation, are required for a chain mechanism to be successful. Some of the most common initiators are di-t-butyl peroxide, t-butyl perbenzoate, dibenzoyl peroxide, and di-t-butyl peroxalate, which can be initiated by either light or heat. Scheme 1-1 features the most common free radical initiator azobisisobutyronitrile (AIBN, **1-1**), which when heated or irradiated with light, undergoes fragmentation to give nitrogen gas and two stabilized tertiary radical species **1-2**. The butyronitrile radical may abstract a hydrogen atom from tributyltin hydride (**1-3**) to give tributyltin radical **1-4** thus initiating a free radical chain mechanism.



Scheme 1-1

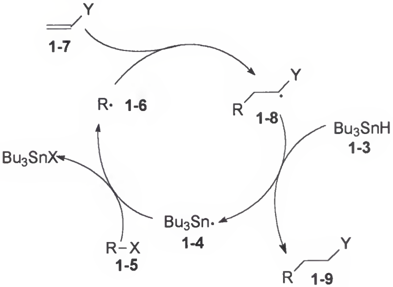
In order for a step to be termed a propagation step, a new radical species must be formed. There are five categories of propagation steps, shown in Scheme 1-2: addition reactions (Eq. 1); elimination (fragmentation) reactions



Scheme 1-2

(Eq. 2); substitution (abstraction) reactions (Eq. 3); electron transfer reactions (Eq. 4); rearrangement reactions (Eq. 5).[1]

There are two main elements, which are important for free radical chain mechanisms: (1) the selectivities (reactivities) of the radical species must differ from one another and (2) the radical recombination rate must be slower than the rate of reaction between radical and non-radical species. Scheme 1-3 illustrates the free radical chain reaction mechanism for an addition propagation step,



Scheme 1-3

where tributyltin radical **1-4** reacts with alkyl halide **1-5** generating a new alkyl radical species **1-6**. Olefin **1-7** then accepts the radical from **1-6**, forming a carbon-carbon bond in radical species **1-8**, where substituent Y is an electron withdrawing group. In order to continue the radical chain mechanism, radical species **1-8** abstracts a hydrogen atom from tributyltin hydride, generating both a new molecule of tributyltin radical and the final substrate **1-9**.

The presence of an electron withdrawing group on the olefin **1-7** allows the reaction to proceed cleanly. Otherwise reactive intermediates **1-6** and **1-8**, both unstabilized alkyl radicals, would have about the same reactivity, therefore polymerization, simple reduction of the alkylhalide, or a mixture of the two processes would occur.[6] One must be careful to choose reactive partners carefully. For instance, an electron rich radical species (substituted with alkoxy, alkyl, or amine groups) would react efficiently with an electron deficient olefin (substituted with ester, ketone, or cyano groups). While, an electron poor radical species would prefer to react with an electron rich olefin.

These tendencies can be rationalized using Frontier Molecular Orbital theory, FMO, (Figure 1-1). The singly occupied molecular orbital (SOMO) in which the radical electron resides prefers to interact with the closest orbital in energy, either the highest occupied molecular orbital (HOMO) or the lowest unoccupied molecular orbital (LUMO).[5] The preference shown in Figure 1-1 is due to the low energy SOMO for the electrophilic radical being in closer proximity to the relatively high energy HOMO for an electron-rich alkene. Also, the high energy SOMO for the nucleophilic radical will prefer to interact with the low energy LUMO of an electron deficient alkene. This concept will be illustrated in Chapter 3, when a nucleophilic radical will only react with an electron poor allyl-stannane reagent.

Another important aspect of the chain reaction mechanism is the relative rates of reduction of intermediate **1-6** and reaction of **1-6** with the olefin. In order to obtain the desired product, the rate of hydrogen atom transfer to substrate **1-6** must be slower than reaction of radical species **1-6** with olefin. Therefore, the concentrations of olefin and hydrogen atom source have to be adjusted according to their reactivities. Another competition reaction must also be considered. In Scheme 1-3, tributyltin radical species **1-4** can either react with the alkyl halide starting material to give the desired product or can add across (hydrostannylate) the double bond of the olefin species. When electron deficient

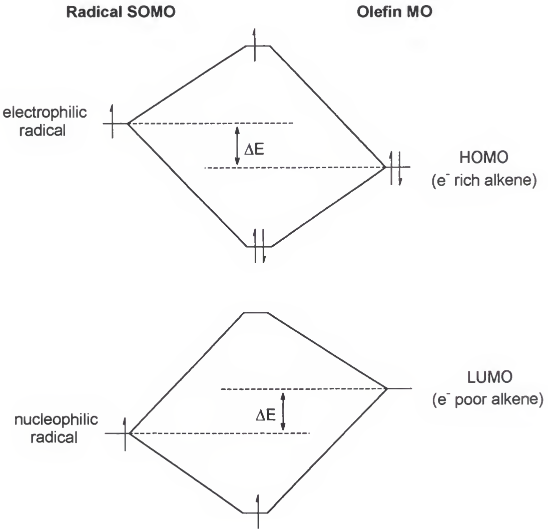
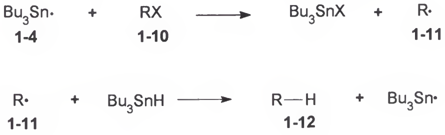


Figure 1-1

olefins and alkyl bromides are used as starting materials, a mixture of desired product and hydrostannylation product results. To circumvent this problem, highly reactive alkyl iodides should be substituted.[7]

In addition to the above discussion on radical additions to alkenes, the more commonly utilized free radical reactions will be discussed in the following paragraphs. Reduction of organic halides is thought to be the most commonly used free radical methodology. Scheme 1-4 illustrates the reduction of an alkyl halide using tributyltin hydride. First, tributyltin radical reacts with alkyl halide **1-10** to form an intermediate alkyl radical species **1-11**. In order to regenerate tributyltin radical and form the final product **1-12**, the alkyl radical species must abstract a hydrogen atom from tributyltin hydride. Thio[8], telluro[9], and seleno[10] compounds are also reduced by tributyltin hydride.

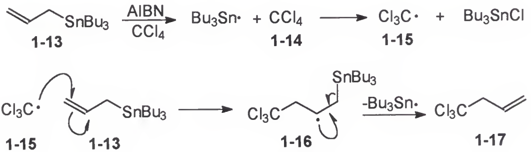


$$\underset{\textbf{1-4}}{Bu_3Sn\cdot} + \underset{\textbf{1-10}}{RX} \longrightarrow Bu_3SnX + \underset{\textbf{1-11}}{R\cdot}$$

$$\underset{\textbf{1-11}}{R\cdot} + Bu_3SnH \longrightarrow \underset{\textbf{1-12}}{R{-}H} + Bu_3Sn\cdot$$

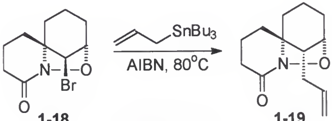
Scheme 1-4

The reaction of polyhalomethanes,such as **1-14**, with allyltributylstannanes **1-13** via a free-radical chain mechanism was first documented in 1973. Scheme 1-5 illustrates the mechanism, in which a small amount of tributyltin radical is generated from the reaction of allylstannane with initiator. Tributyltin radical can then abstract a halogen atom from the substrate, generating an electron deficient radical center in **1-15**, which subsequently reacts with the olefin of allyl stannane. Elimination of tributyltin radical from radical species **1-16** then provides the final allylated product **1-17**.



Scheme 1-5

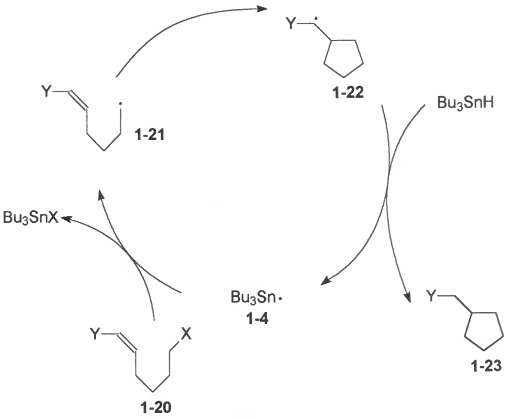
This methodology was not applied to nucleophilic alkyl radicals until a decade later, through the work of Keck.[11] Halides, as well as phenylselenides and xanthates, were reacted with allylstannane and AIBN as the initiator. Scheme 1-6 is an example of a bromide being replaced by an allyl group.



Scheme 1-6

Many examples are now known of this extremely useful method of allylation, which shows the same compatability with labile functional groups and molecular complexity as typical tributyltin hydride chemistry.

Even though the first ring formation by tributyltin hydride in the synthesis of natural products was the formation of a six-membered carbocyclic ring, free radical cyclizations are most often applied to the formation of five-membered rings.[12] One main reason for the above trend is five-membered rings form almost fifty times faster than six-membered rings. Therefore, the formation of the smaller ring is less affected by unwanted side reactions, such as simple



Scheme 1-7

reduction of starting material or other uncyclized biproducts.[13] Scheme 1-7 illustrates the free radical chain mechanism for carbocyclic ring formation. The cyclization of 5-hexenyl radical **1-21** to cyclopentylmethyl radical **1-22** occurs at a rate of approximately 10^6 (s^{-1}) at room temperature, and increases with an electron deficient olefin.[14]

At first glance the selectivity requirement for radical chain mechanisms is not fulfilled. Radical intermediates **1-21** and **1-22** do have nearly identical reactivities, however, intermediate **1-21** reacts intramolecularly with the double bond, while intermediate **1-22** reacts in a intermolecular fashion with tributyltin radical. With the intramolecular ring closure reaction occurring more quickly than hydrogen atom transfer, the selectivity requirement is fulfilled.

Why is the less stable primary radical formed more readily than the more stable secondary radical? According to Baldwin,[15] exo-cyclizations, which account for cyclopentyl product, are favored over endo-cyclizations, which lead to the cyclohexenyl product. Less favorable entropies[16] for the formation of cycloalkyl radicals, and steric effects in the 6-endo cyclization transition state, such as, 1,3 diaxial interactions,[17] also account for the favored formation of 5-exo cyclization product.

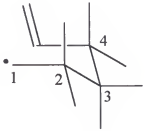


Figure 1-2

A set of guidelines for predicting stereochemical outcome in 5-exo cyclizations has been formulated by Beckwith.[18] First, cis-disubstituted cyclopentyl products are favored when the 5-hexenyl radical species is substituted at positions 1 or 3 (Figure 1-2). Secondly, substituents at positions 2 or 4 lead to mainly trans-disubstituted cyclopentyl products. A few examples, which illustrate the utility of Beckwith's guidelines, are shown in Table 1-1.

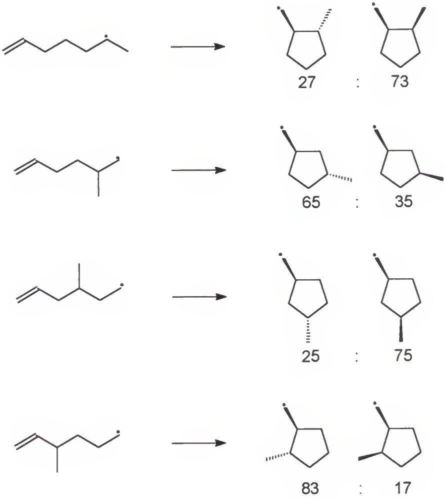
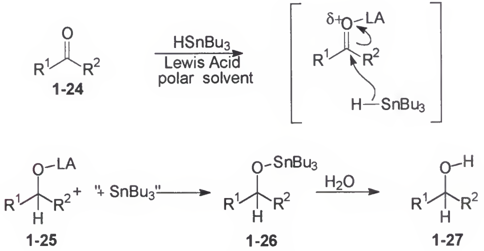


Table 1-1

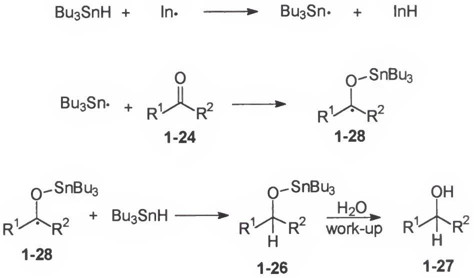
Another common application of tributyltin hydride reagent is the reduction of carbonyl compounds. As mentioned earlier, tributyltin hydride can hydrostannylate double bonds such as alkenes. Therefore, it is not surprising that tin hydride can hydrostannylate another form of sp^2 hybridized bonds, aldehydes and ketones. After hydrostannylation is completed to form the tin alkoxide, the weak tin oxygen bond is easily hydrolysed by water to provide alcohol **1-27**. Depending on the conditions utilized, two possible mechanisms have been postulated.

When a Lewis acid (LA) is utilized to activate the carbonyl, an anionic mechanism (Scheme 1-8) applies. Simply, a hydride is delivered from tributyltin hydride to the activated carbonyl to formally give tributyltin cation and alkoxy anion, which lead to tin alkoxide **1-26**. Subsequent hydrolysis of the tin-alkoxide bond provides the alcohol. Scheme 1-9 illustrates a radical mechanism,[19] where an initiator first abstracts a hydrogen atom from tributyltin hydride to form tributyltin radical. Tributyltin radical then reacts with the carbonyl substrate **1-24** to give O-stannyl ketyl **1-28**, which then abstracts a hydrogen atom from



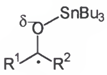
Scheme 1-8

tributyltin hydride, in order to continue the free-radical chain mechanism. Once the tin alkoxide **1-26** is formed, simple water work-up provides alcohol **1-27**.



Scheme 1-9

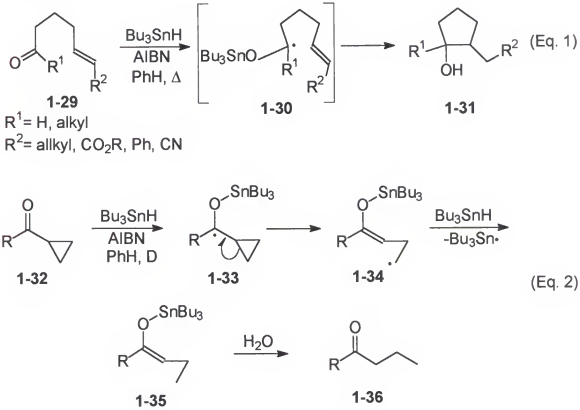
The experimental conditions that lead to an anionic mechanism involve Lewis acids[20] and polar solvents, such as methanol,[21] or a highly reactive electrophilic carbonyl substrate. On the other hand, when the reaction is initiated with AIBN or hυ,[21,22] the radical mechanism is followed.



1-28

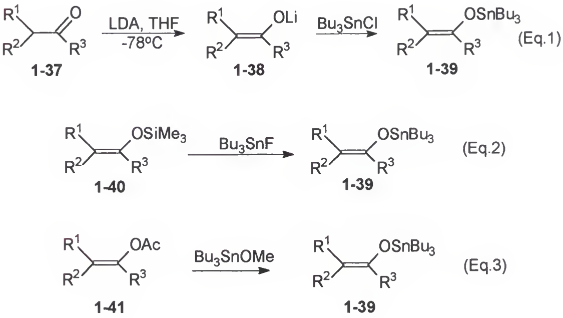
Figure 1-3

A key intermediate in the radical mechanism for reduction of carbonyls is O-stannyl ketyl **1-28** (Figure 1-3), which exhibits radical character at the carbonyl carbon and partially negative character on the oxygen, due to the electronegativity difference between tin and oxygen. ESR (electron spin resonance) studies[23] have shown that nearly 70% of the unpaired electron density resides on the carbon, therefore the carbon centered radical can react with electron acceptors (Scheme 1-10, Eq. 1) or can open strained rings (Eq. 2).[24]



Scheme 1-10

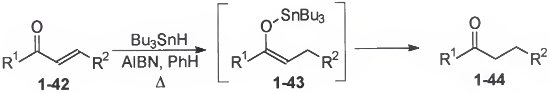
Since the majority of this dissertation discusses new applications of O-stannyl enolates, a short introduction is in order. Traditional routes to O-stannyl enolates typically involved harsh conditions, such as Li/NH_3 reduction, and strong bases, such as lithium diisopropyl amide. A few pathways to O-stannyl enolates are depicted in Scheme 1-11. Equation 1 shows the most commonly used route, where ketone **1-37** is deprotonated with lithium diisopropyl amide to provide lithium enolate intermediate **1-38**. Trans-metalation with tributyltin chloride then gives the O-stannyl enolate **1-39**. Another route involves the deprotection of silyl enol ether **1-40** with fluoride ion[25] (Eq. 2) to provide the intermediate enolate; subsequent coordination with positively charged tributyltin provides the O-stannyl enolate **1-39**. Lastly, enol acetates can be deprotected with tributyltin methoxide[26] to provide an enolate intermediate and acetonyltributyltin; further reaction then furnishes the O-stannyl enolate. Nearly all of the traditional methods of tin enolate formation require at least two steps from the carbonyl compound and many of the examples require the use of a



Scheme 1-11

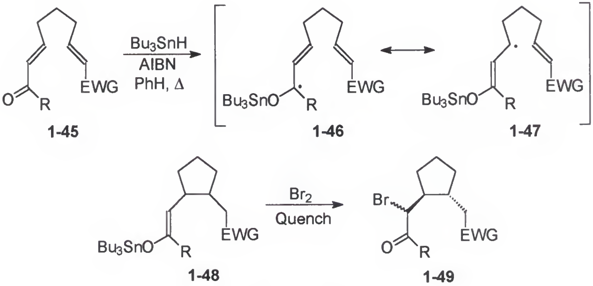
strong base. Therefore, a method for *in situ* formation of O-stannyl enolates via neutral free radical methods would be a tremendous advantage.

In the late 1960s researchers discovered that reduction of α,β-unsaturated carbonyls leads to the reduction of only the olefin (Scheme 1-12).



Scheme 1-12

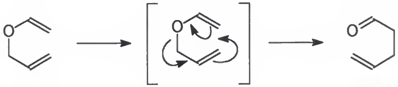
An organotin enol ether[27] **1-43** was the postulated intermediate, however no one took advantage of this direct route to O-stannyl enolates until the early 1990s. Enholm and co-workers[28] first applied the *in situ* formation of O-stannyl enolates to radical ring closures (Scheme 1-13). The presence of an enolate was proven by quenching the intermediate with Br_2, which leads to bromination α to the carbonyl in **1-49**.



Scheme 1-13

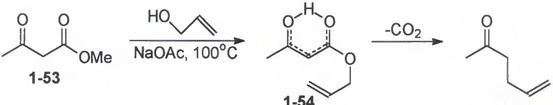
[3,3]-Sigmatropic Rearrangements

A major portion of this dissertation discusses a new unprecedented free radical approach to accelerated Claisen rearrangements. Therefore, an introduction to the areas of sigmatropic and charge accelerated rearrangements is appropriate. The Claisen rearrangement was first discovered in 1912 by the reaction's name-sake,[29] and more recently the sigmatropic rearrangement has become the one of the most powerful tools for stereoselective carbon-carbon bond formation.[30] Scheme 1-14 depicts the simple allyl vinyl ether **1-50** used in the first Claisen rearrangement, where extremely high temperatures were required for product formation. A base catalyzed condensation / rearrangement (Scheme 1-15) of β-keto esters **1-53** with allyl alcohol to yield alkenic ketones **1-55** was developed in 1940 by Carroll,[31] and requires a temperature of only 100°C.



1-50 **1-51** **1-52**

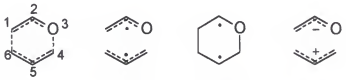
Scheme 1-14



1-53 **1-54** **1-55**

Scheme 1-15

Claisen rearrangements are exothermic,[32] concerted, pericyclic reactions with a negative entropy, due to the formation of a stable carbonyl functionality. Gajewski and coworkers[33] utilized deuterium labeling to find an early transition state, where bond breaking is more advanced than bond formation. There is disagreement over which of the structures (Scheme 1-16) –aromatic (**1-56**),[34] oxaallyl radical allyl radical pair (**1-57**), 2-oxacyclohexane-1,4-diyl (**1-58**), or dipole (**1-59**)- most accurately represents the transition state structure.[35]



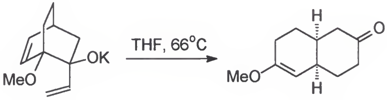
1-56 **1-57** **1-58** **1-59**

Scheme 1-16

Resonance stabilizing substituents would be an important factor for any of the possible intermediate structures, whereas electron donating and withdrawing substituents would have the greatest affect on the dipole transition state.

The effect of donor and acceptor substituents on rates of sigmatropic rearrangements has been the subject of many investigations. These experiments inspired the development of Carpenter's[36] model for predicting substituent effects on the acceleration of various sigmatropic rearrangements. According to the model, which is based on HMO calculations, acceleration should be observed for electron acceptors at positions 2 and 4 and electron donor groups at position 1. While, electron accepting substituents at positions 1 and 6 and electron donor groups at positions 5 and 6 have a negative affect on the rate of the rearrangement. To test the model, five isomeric cyano substituted allyl vinyl ether substrates where synthesized and investigated. All of the predictions for Carpenter's model where fulfilled. However, when trifluoromethyl substituents where utilized, trends conflicting with the model predictions were observed. A trifluoromethyl substituted at position 2 showed an enhanced rate compared to the parent system, while substitution at position 4 showed no change, indicating the "radical-stabilizing" rather than the "electron-withdrawing" ability contributes to the stabilization of the transition state.

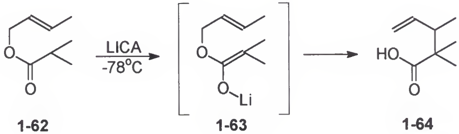
The investigations in the area of charge accelerated sigmatropic rearrangements are more straightforward and less argumentative. *Ab initio* calculations and estimated bond dissociation energies[37] led to the finding that oxyanion substituents tend to weaken the adjacent carbon-carbon bond. Carpenter[36] found that cationic, anionic, and radical substituents accelerate the rearrangement by increasing the charge delocalization in the transition state, where the array of orbitals is completely conjugated. Illustrating the utility of an anionic substituent, a rate increase of nearly 10^{15} was reported for an oxy-Cope[38a] rearrangement (Scheme 1-17), where the potassium salt of dienol



1-60 **1-61**

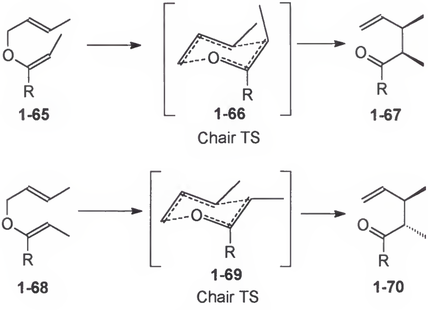
Scheme 1-17

1-60 rearranges to provide ketone **1-61**. Also, Ireland and Mueller[38b] found that lithium enolate derivatives of allyl esters undergo Claisen rearrangements at ambient temperatures (Scheme 1-18).



Scheme 1-18

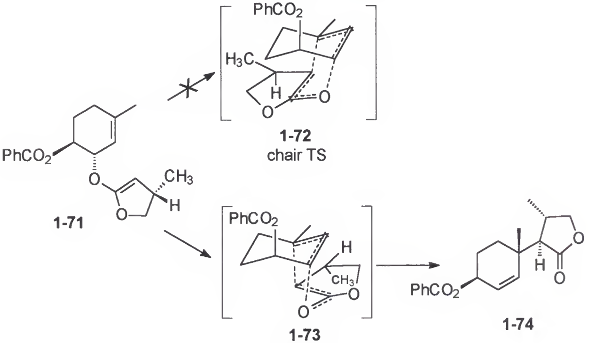
Transition state geometry is another important aspect of sigmatropic rearrangement mechanisms. There are five possibilities[39] for transition state geometry for the Claisen and the similar Cope rearrangements: boat, chair,



Scheme 1-19

twist-boat, cross and plane. The twist-boat, plane, and cross geometries are highly unlikely, since extremely high temperatures would be required to give these intermediates. Overwhelming evidence exists for a preference for chair-like transition states when acyclic systems are studied. For example, the allyl vinyl ethers **1-65** and **1-68** (Scheme 1-19) have a 97-98% selectivity for the chair transition state, which translates to a 3 kcal mol^{-1} difference between the energy of activation of the chair and boat transition states.

The boat transition state geometry becomes more likely when conformational constraints in cyclic precursors override the preference for the chair-like transition state. Lythgoe and coworkers[40] found that steric interaction between the methyl group and the cyclohexane ring in the chair conformation

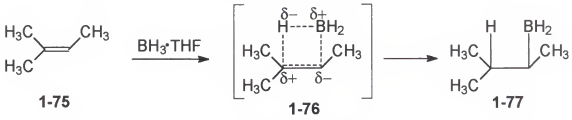


Scheme 1-20

1-72 (Scheme 1-20) results in a preference for the boat conformation, giving exclusively product **1-74**.

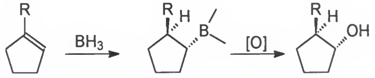
Hydroboration

Chapter four of this dissertation involves the development of new methodology for the transformation of α,β-unsaturated ketones to trans-diols via the hydroboration of O-stannyl enolates. The following paragraphs will provide a brief introduction to the area of hydroboration. The borane reagent is an electron deficient compound with six valence electrons, where the central atom, boron, lacks an octet. This extremely electrophilic reagent prefers to react with electron rich double bonds leading to anti-Markovnikov products. Gaseous diboranes only react under extreme conditions,[41] however in the presence of ethers, such as diethyl ether and tetrahydrofuran, the reaction proceeds more efficiently. In tetrahydrofuran for instance, borane is known to exist primarily in monomeric form and forms stable solutions at moderate concentrations.



Scheme 1-21

In the transition state (Scheme 1-21), borane adds to the olefin in one step, where the hydride adds to the most substituted carbon and boron adds to the least substituted carbon. This orientation places the partially positive charge on the more highly substituted carbon, therefore creating a more stable transition state. Also apparent from the transition state drawing, the hydride and boron add syn across the double bond and prefer to add to the least sterically encumbered face of the olefin. Also, all three of the hydrides from BH_3 are used in hydroboration, resulting in a trialkylated borane intermediate. Upon oxidation the three alkyl groups are released as alcohols.



1-78 **1-79** **1-80**

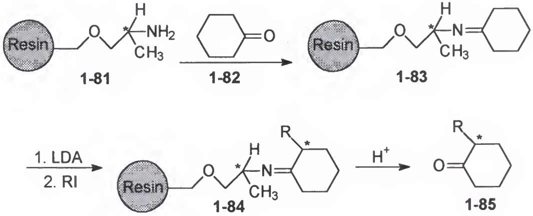
Scheme 1-22

The hydroboration of cyclic substituted olefins results in an anti relationship between the boron and the substituent.[42] This concept is illustrated in Scheme 1-22, where 1-alkylcyclopentene **1-78** undergoes hydroboration to give trans-borane intermediate **1-79**. Upon oxidation, trans alcohol **1-80** is observed as a result of oxidation, which proceeds with retention of configuration.

Solid Phase Organic Synthesis

Chapter five of this dissertation introduces a new solid phase bound allylstannane reagent. The following paragraphs will present a brief introduction to the relatively unexplored area of solid phase organic chemistry (SPOC). Merrifield,[43] the father of solid phase chemistry, developed a resin bound synthesis of polypeptides over three decades ago. Until recently, the solid phase synthesis of non-polypeptides has received little attention.[44]

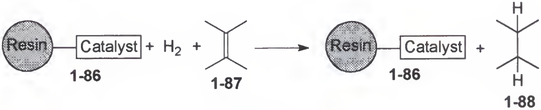
There are two distinct categories of solid phase organic synthesis: polymeric protecting groups and polymer bound reagents. Reactions utilizing polymeric protecting groups involve linking a starting substrate to the resin via a linker and subsequent derivatization of another site on the substrate. Once the series of reactions is completed, the substrate must be removed from the resin.



Scheme 1-23

Scheme 1-23 is an example of a synthesis on solid support, where homo chiral 2-alkylcyclohexanone **1-85** is synthesized by a solid phase enamine reaction.[45] There are many advantages to using a polymeric protecting group for the synthesis of organic compounds, such as: (1) little purification is required, (2) excess reagent can be used to force the reaction to completion, (3) the solid support can be regenerated in most cases, and (4) automated synthesis is possible.

Reactions with polymer bound reagents involve a one-step reaction in which the dissolved substrate reacts with chemical reagents (mostly catalysts or enzymes)[46] that are attached to polymer resin. Scheme 1-24 is a representation of a one step reaction of a polymer bound catalyst. The advantages of using polymer bound reagents are as follows: (1) the reagent will not contaminate the substrate, (2) the resin can often be reused, and (3) the template effect in asymmetric synthesis can be taken advantage of. The resin bound reagent is especially useful when a toxic reagent is required for the synthesis of a drug. Among the many examples of resin bound reagents are hydrogenation catalysts, triarylphosphines,[47] oxidizing and reducing reagents, chiral auxiliaries and catalysts.[45]



Scheme 1-24

This dissertation discusses three new synthetic organic methodologies, which take advantage of *in situ* formation of O-stannyl enolates and also the synthesis of a novel resin bound allylstannane reagent. The new methodologies utilize neutral free radical chemistry to accelerate sigmatropic rearrangements, to form carbon-carbon bonds β to carbonyls, and lastly to synthesize trans-diols from enones.

Chapter 2 presents an unprecedented ketyl triggered [3,3] sigmatropic shift, where two additional reactive sites in the intermediate, a carbon centered radical and electron rich oxygen tin bond, offer the option of tandem functionalization. Several examples will be discussed along with synthesis of Claisen rearrangement precursors. A mechanistic investigation was undertaken to determine whether hydrogen atom transfer to a radical center or sigmatropic rearrangement is occurring first.

Chapter 3 examines the reaction of an electron rich carbon centered radical with an electron deficient allyl stannane reagent. This new methodology is a neutral alternative to cuprate chemistry, where a carbon-carbon bond is formed β to a carbonyl.

Chapter 4 involves the development of methodology in which O-stannyl enolates are hydroborated to give, after oxidation, trans-diols. This represents the first one-pot transformation of α,β-unsaturated carbonyls to trans-diols. Several cyclic examples will be given, along with an acyclic example, which curiously leads to only mono-alcohols.

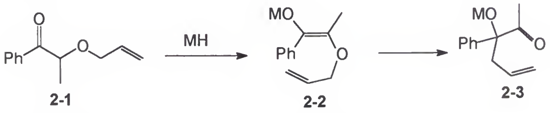
Chapter 5 examines the synthesis of a resin bound allylstannane reagent. Several plausible routes were investigated, leading to a route based on the synthesis of a recently discovered resin bound tin hydride reagent. The synthesis of the reagent and an example of allyl transfer to an alkylhalide will be discussed.

CHAPTER 2
A KETYL RADICAL-ANION "TRIGGERED" [3,3]-SIGMATROPIC SHIFT

Introduction

One of the most utilized pericyclic rearrangements in organic synthesis is the internal allyl transfer in the [3,3] sigmatropic shift or Claisen rearrangement.[48] A more recent innovation involves the incorporation of a charge in the intermediate, which accelerates the rearrangement; therefore the reaction occurs at reduced temperatures. Examples of charge accelerated sigmatropic rearrangements include the use of metal enolates, alkoxides, and silyl ketene acetals as intermediates. One electron donors such as tributyltin hydride and samarium diiodide have the potential to introduce a charge into the array of atoms undergoing a rearrangement,[49] while at the same time avoiding the use of harsh bases. A metal-associated enolate, readily obtained by the partial reduction of an α,β-unsaturated ketone by a one-electron donor, has the potential to initiate a [3,3]-sigmatropic rearrangement.

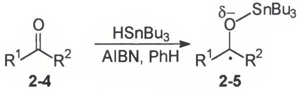
The origin of this work was the development of an anionic oxy-Claisen rearrangement of enolates of α-allyloxy ketones (Scheme 2-1) in the mid-80s by Koreeda and co-workers.[50] Several different metals and solvents were investigated, which led to the observation that the efficiency of the reaction is influenced by the metal counter ion as well as the solvent. Large amounts (15 eq.) of strong base were generally required for the efficient formation of the rearrangement product.



Solvent	Metal	Temp., (C°)	Half-Life (h)
Toluene	K	-23	3.3
Toluene	Li	96.5	1.1
THF	K	-23	<0.1
THF	Li	67	1.3

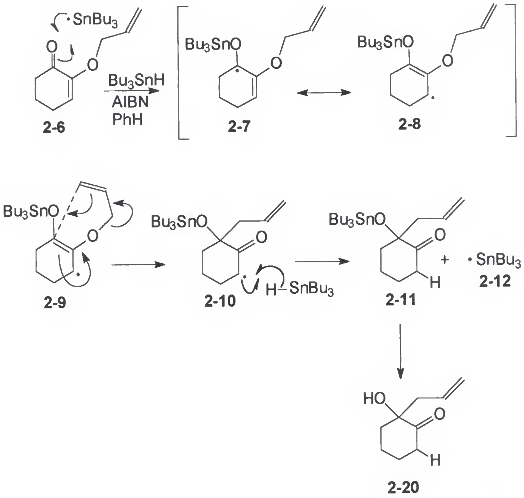
Scheme 2-1

The following investigation will show that Claisen rearrangements are triggered by the formation of O-stannyl ketyls **2-5** (Scheme 2-2). This new methodology offers a mild alternative to the harsh conditions methods used previously. It is noteworthy that a carbon-carbon bond is formed at the expense of a carbon-oxygen bond in a Claisen rearrangement. Also, the transition state



Scheme 2-2

for [3,3]-sigmatropic rearrangements follows a predictable chair-like geometry (Scheme 1-18).



Scheme 2-3

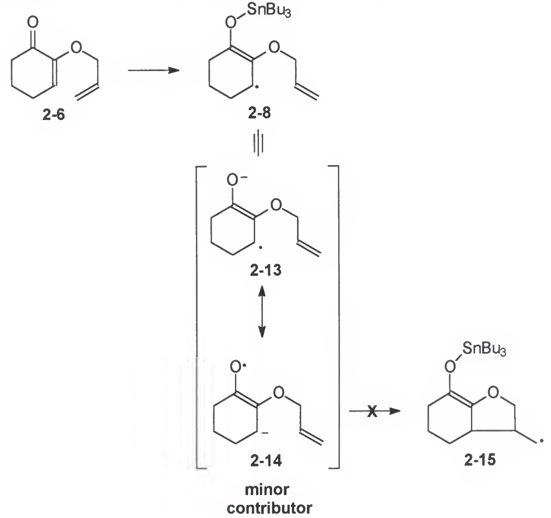
The reaction we studied represents an unprecedented tributyltin hydride initiated-anionic accelerated Claisen rearrangement, as well as the first example of a radical-anion used to drive a sigmatropic rearrangement. The starting substrate **2-6** for the radical-anion mediated Claisen rearrangement, shown in Scheme 2-3, consists of an α,β-unsaturated carbonyl functionality with an olefin tethered to the enol. A reaction under free-radical conditions provided an allylic

O-stannyl ketyl **2-7**, which is in resonance with O-stannyl enolate radical species **2-8**. According to Carpenter's[35] model a charged or radical substituent has the potential to accelerate a sigmatropic rearrangement, since in both cases the transition state is stabilized. O-stannyl enolate radical species **2-8** possesses both radical and anionic sites, therefore offering transition state stability from two sites. One could speculate that the radical could possibly increase the reaction rate compared to enhancement from an anion alone. The electron rich O-stannyl enolate radical species features two tethered olefins in a 1,5 orientation, therefore, an accelerated Claisen rearrangement should follow to give tin(IV) alkoxide, **2-10**. Note the radical is delocalized in **2-10**. Hydrogen atom transfer from tributyltin hydride to the radical site, followed by water work-up should prepare alcohol **2-20** as the final product.

One potential problem with the methodology is evident upon examination of enolate intermediate **2-8**. A possible 5-exo-trig radical ring closure between the β-radical center and the olefin is apparent. A closer look at the resonance structures for the enolate intermediate (Scheme 2-4), leads to two main resonance contributors **2-13** and **2-14** where a negative charge resides on the β-carbon. Therefore, the radical is nucleophilic and will not react with the electron rich alkyl-substituted olefin.

The following work will show several examples of this novel ketyl radical-anion initiated [3,3] sigmatropic rearrangement, which was conducted entirely at 80°C under neutral free radical conditions.[51] Treatment of **2-6**[52] with 1 equivalent of tributyltin hydride and AIBN followed by a reflux period of 3 hours afforded **2-**

20 in approximately 74% yield. Other substrates were studied as well, and are shown in Table 1. Examination of the ^{1}H and ^{13}C NMRs of products **2-21** and **2-22** indicate that only one diastereomer was present in each case. In order for this methodology to be more widely applicable, an acyclic precursor was also investigated. Acyclic compound **2-18** reacted to form **2-23** in only 51% yield; the low yield may be attributed to the formation of eliminated product, since elimination results in a conjugated system. To avoid formation of eliminated



Scheme 2-4

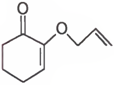
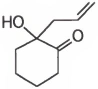
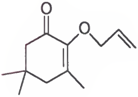
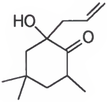
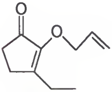
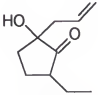
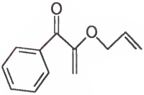
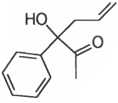
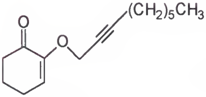
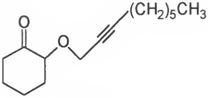
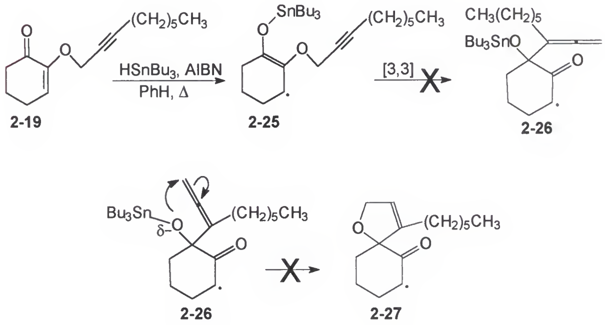
Starting Substrate	Product	Yield
 **2-6**	 **2-20**	**74%**
 **2-16**	 **2-21**	**62%**
 **2-17**	 **2-22**	**62%**
 **2-18**	 **2-23**	**51%** **61%** Catalytic Cond.
 **2-19**	 **2-24**	**70%**

Table 1

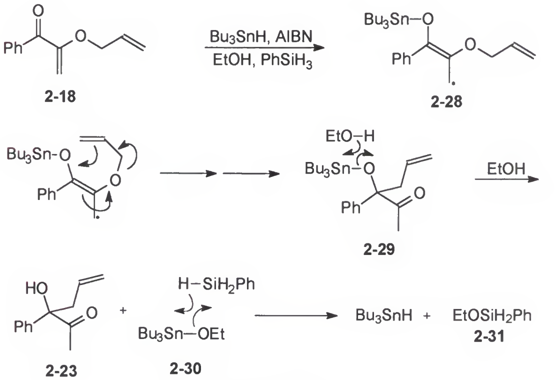
product, a catalytic tin method[53] developed by G. Fu was investigated, and the yield of product was increased slightly to 61%.

To expand the applications of the ketyl "triggered" Claisen method, an acetylenic system **2-19** was subjected to free-radical conditions. Even though an allene intermediate **2-26** (Scheme 2-5) was expected, possibly resulting in a second rearrangement, only reduced product was isolated. Claisen rearrangements of acetylenic compounds[54] are documented, but in this case the sp hybridized carbons of the acetylene tether may not be able to attain the proper 6-membered transition state geometry required for the Claisen rearrangement.



Scheme 2-5

Industry, especially pharmaceutical, is concerned with the toxicology of trialkyltin hydrides and is reluctant to utilize this very useful reagent. The development of catalytic conditions for the use of tributyltin hydride would be a tremendous advantage and would make free radical methods more available to industry. Fu and co-workers[53] developed conditions, which only require 0.2 equivalents of tributyltin hydride. Also, using these conditions tributyltin hydride can theoretically be recovered and reused. Phenyl silane and ethanol are thought to be responsible for the regeneration of tributyltin hydride. Scheme 2-6

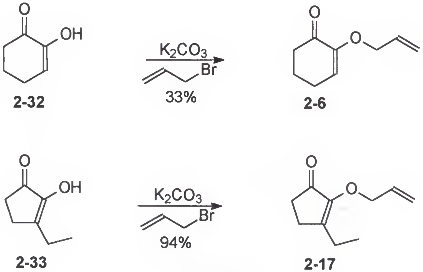


Scheme 2-6

illustrates the proposed mechanism of enolate formation, Claisen rearrangement and tributyltin hydride regeneration. First, O-stannyl enolate **2-28** is formed under free-radical conditions. Subsequent Claisen rearrangement provides tertiary tin alkoxide **2-29**, which Fu believes is too sterically hindered to react directly with bulky phenyl silane. Therefore, ethanol must exchange with the tertiary tin alkoxide to provide primary tributyltin ethoxide (**2-30**) and the desired product **2-23**. Tributyltin hydride is now regenerated by reaction of tributyltin ethoxide and phenyl silane. Only one third of an equivalent of phenyl silane is required since each phenyl silane molecule possesses three available hydrogens.

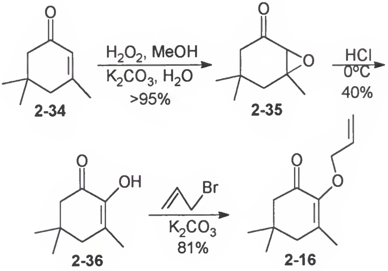
Synthesis of [3,3]-Sigmatropic Shift Precursors

Substrates **2-6** and **2-17** were synthesized by allylation of the appropriate commercially available dione, as shown in Scheme 2-7. Allylation of cyclohexanedione resulted in low yield of enol ether; most likely due to competition of carbon alkylation. Enol ether **2-16** was synthesized by

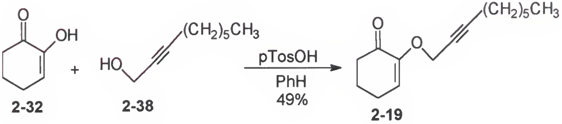


Scheme 2-7

epoxidation of isophorone,[55] subsequent opening of the epoxide[56] with concentrated hydrochloric acid and allylation[57] of the resulting enol **2-36** (Scheme 2-8). A simple condensation reaction between 2-nonyn-1-ol (**2-38**) and cyclohexanedione gave enol ether **2-19** (Scheme 2-9).



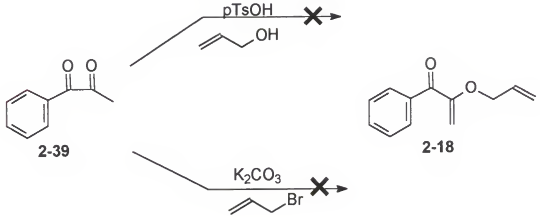
Scheme 2-8



Scheme 2-9

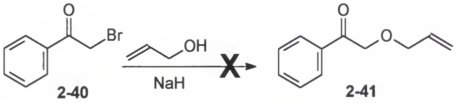
The first approach to the synthesis of the acyclic precursor **2-18** involved a simple enol ether synthesis from the diketone species **2-39**. As Scheme 2-10 shows, Williamson ether synthesis conditions did not give the desired product.

Other conditions were investigated, such as with lithium hexamethyl disilizane and under acidic conditions, and were not successful.

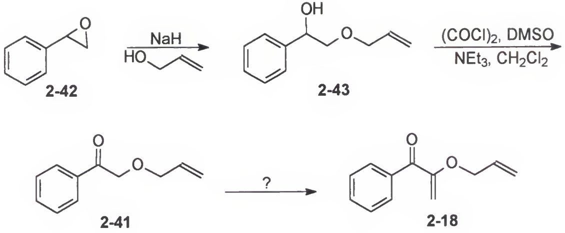


Scheme 2-10

A more inefficient route was then investigated, where the synthesis of α-allyloxy ketone **2-41** (Scheme 2-11) was undertaken, since there are many ways to install an exomethylene α to a carbonyl. First, a reaction between allyl alcohol and bromoacetophenone (**2-40**) was attempted and gave several products, with no indication of the desired product. A two step synthesis (Scheme 2-12) where styrene oxide was opened with allyloxy anion to give the alcohol, then subsequent oxidation utilizing Swern[58] conditions was successful. The installation of the exomethylene can be accomplished in a variety of ways,

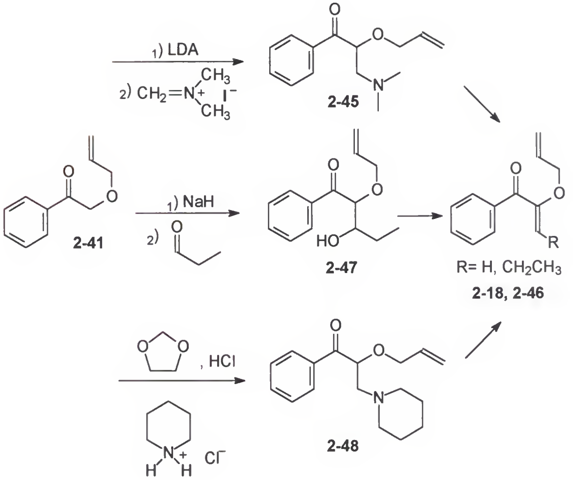


Scheme 2-11



Scheme 2-12

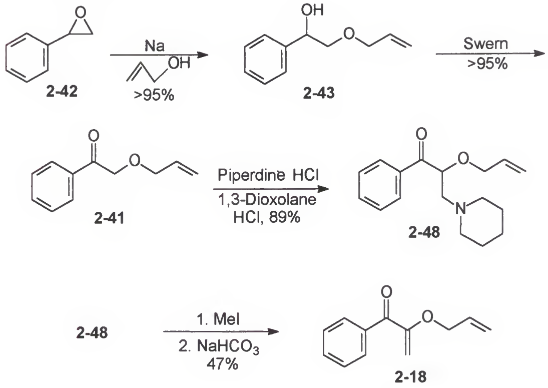
shown in Scheme 2-13. Deprotonation α to the carbonyl of **2-41** with lithium diisopropyl amide and condensation with Eschenmoser's salt should give Mannich base **2-45**, which after quaternization and elimination should provide the desired exomethylene. However, the reaction of α-allyloxy ketone **2-41** with lithium diisopropyl amide resulted in the formation of several products. Several different bases were utilized, however the desired product was never isolated. Aldol condensation reaction and elimination would also provide the desired α,β-unsaturated carbonyl substrate, but the reaction to give alcohol **2-47** was unsuccessful. A literature search unearthed an acidic method for the formation of a Mannich base. Ohno and co-workers[59] found that dioxolane, piperidine hydrochloride, and hydrochloric acid form an Eschenmoser salt *in situ*, while also forming the enol from the carbonyl. Reaction of the enol with the Eschenmoser



Scheme 2-13

salt then provides the Mannich base **2-48**, which when quaternized can eliminate to furnish α,β-unsaturated ketone **2-18**.

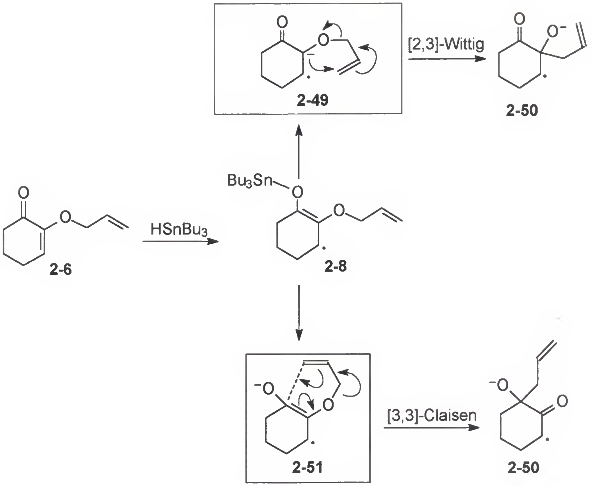
Scheme 2-14 illustrates the entire synthetic route for the formation of **2-18**. The reaction of styrene oxide with allyl alcohol gave alcohol **2-43**. Oxidation of the alcohol using Swern conditions provided allyloxy ketone **2-44**. Using the acidic conditions developed by Ohno and coworkers, the Mannich base **2-48** was provided. With the Mannich base in hand, a simple quaternization of the amine[60] with methyl iodide and elimination gave the desired α,β-unsaturated carbonyl compound, **2-18**.



Scheme 2-14

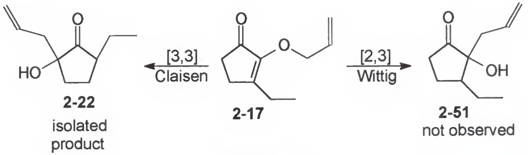
Mechanistic Considerations

For the rearrangement of precursor **2-6**, two sigmatropic rearrangement modes (Claisen and [2,3]-Wittig) lead to the same product, shown in Scheme 2-15. O-stannyl enolate **2-8** can be viewed as an α-allyloxy α-carbanion, which is capable of undergoing a [2,3]-Wittig rearrangement giving rise to the α-alkoxy ketone **2-50**. While the resonance structure with the anionic charge localized



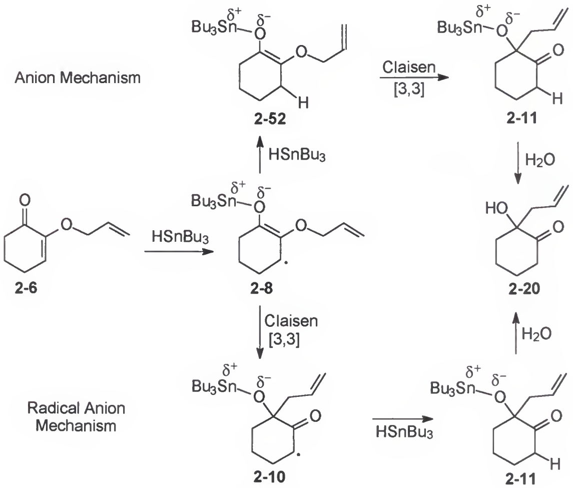
Scheme 2-15

on the oxygen can be envisioned as a 1-oxyanion-3-oxa-1,5-hexadiene and is poised for an anionic accelerated Claisen rearrangement, providing the same product. However, the two rearrangement modes give rise to isomeric products for precursors **2-16**, **2-17**, and **2-18**, therefore allowing the determination of the correct mechanism for the ketyl triggered sigmatropic shift. Scheme 2-16 illustrates the two different products for the two possible mechanisms, where the product formed by the Claisen rearrangement mode corresponds with the product isolated from the free-radical mediated sigmatropic rearrangement.



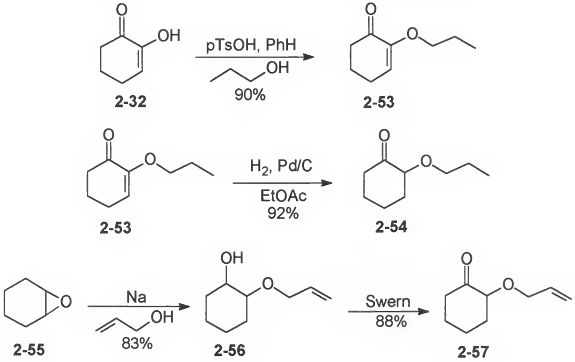
Scheme 2-16

There are two possible mechanistic pathways which would provide the rearranged product **2-20**. Scheme 2-17 outlines both possibilities, where the top pathway illustrates the "Anion Mechanism" in which a hydrogen atom is



Scheme 2-17

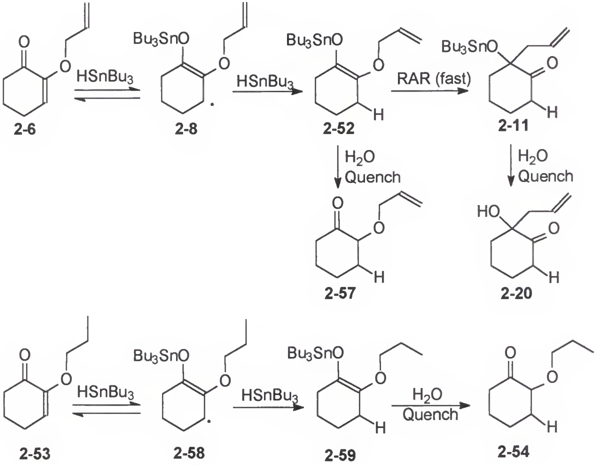
delivered before rearrangement, providing an anionic intermediate **2-52** for the rearrangement step. The bottom pathway shows the "Radical-Anion Mechanism," in which a hydrogen atom is delivered after the rearrangement step, requiring the formation of a radical-anion rearrangement intermediate **2-8**. In order to ascertain the sequence of events and the key intermediates involved in this reaction, a mechanistic study was undertaken. Several substrates were synthesized (Scheme 2-18) in order to accurately monitor the appearance and disappearance of key intermediates during the course of the reaction. Enone **2-53** was synthesized by a condensation reaction between 1,2-cyclohexanedione (**2-32**) and n-propyl alcohol. In order to synthesize substrate **2-54**, a simple hydrogenation was carried out on enone **2-53**. Allyl ether **2-57** was synthesized



Scheme 2-18

by first opening cyclohexene oxide with allyl alcohol under basic conditions to yield **2-56** and subsequent Swern oxidation.

A study of the relative rates of reactions of enol ether **2-6** and substrate **2-53** with tributyltin hydride could shed light on the sequence of hydrogen atom transfer and rearrangement steps. Measuring the rate of formation of **2-59** or the quenched version **2-54** (Scheme 2-19) will approximate the combined rates of tributyltin enolate formation and hydrogen atom transfer for the "Anion Mechanism" for reaction of enol ether **2-6**. This is a reasonable assumption



Scheme 2-19

since the only difference between the two substrates (**2-6** and **2-53**) is an olefin, which is far removed from the sites participating in the reduction. Of course, water quenching of the radical intermediate **2-58** (Scheme 19) leads to formation of **2-54**, which leads one to believe the rate of reaction of **2-53** would only be the rate of tributyltin enolate formation. However, a chain reaction mechanism is required and the reaction would not go to completion unless the hydrogen atom is transferred to regenerate tributyltin radical. Therefore, the rate of formation of **2-54** is a good approximation of the combined rates of tin enolate formation and hydrogen atom transfer for the "Anion Mechanism" for reaction of enol ether **2-6**.

The reactions of **2-6** and **2-53** were conducted in the same reaction vessel to insure identical reaction conditions. Aliquots were removed from the reaction every 30 minutes and quenched with water. Gas chromatography revealed the relative amounts of substrates present in the reaction mixture. Formation of substrate **2-57** was not observed even in trace amounts at any time in three runs of the study, indicating that intermediate **2-52** is not being formed during the course of the reaction. The alternative "Radical-Anion Mechanism" is therefore supported by this finding. In three runs of the competitive mechanistic study the rate of formation of **2-20** was considerably faster than the formation of substrate **2-54**, shown in Fig. 2-1. If the reaction follows the "Anion Mechanism", the formation of Claisen product **2-20** should occur at the same rate as the formation of simple reduction product **2-54**. The rate of the Claisen rearrangement step should not contribute to the rate of the overall reaction, since the rearrangement occurs rapidly. On the other hand if the mechanism follows the "Radical-Anion" mechanistic pathway, a hydrogen atom is being delivered to a more reactive acyl radical species **2-10** (Scheme 2-17); only two resonance structures can be drawn. Therefore, the hydrogen atom transfer for the "Radical-Anion Mechanism" should be faster than for the reduction of substrate **2-53** (which approximates the rate of the "Anion Mechanism"). This is the first example of a sigmatropic rearrangement intermediate containing both anionic and radical sites.

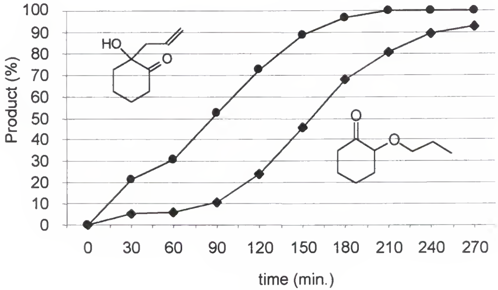
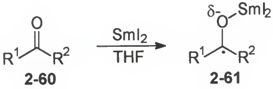


Figure 2-1

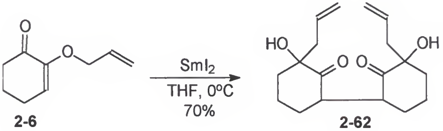
SmI$_2$ Mediated Sigmatropic Rearrangement

Another one-electron donor, Samarium diiodide has the potential to trigger an anionic accelerated sigmatropic rearrangement. Even though both tributyltin hydride and samarium diiodide react with carbonyls to form ketyls, they do so via different mechanistic pathways. While tributyltin hydride and initiator forms ketyls by a free radical chain mechanism as illustrated in Scheme 1-7, samarium diiodide is oxidized to the more stable samarium(III) species while the carbonyl is reduced to form the metal associated ketyl[61] (Scheme 2-20). The samarium diiodide ketyl has enjoyed a variety of chemical transformations, including ring formations, alkylations, ring openings, heteroatom abstractions, pinacol couplings, but has never been utilized to trigger a sigmatropic rearrangement.



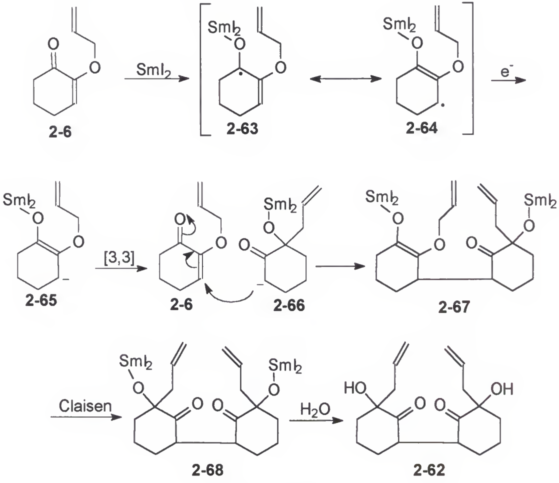
Scheme 2-20

Since, the use of samarium diiodide is more acceptable for industrial applications, a samarium diiodide mediated sigmatropic rearrangement was investigated, as shown in Scheme 2-21. Reaction of enol ether **2-6** with two equivalents of samarium diiodide in tetrahydrofuran at 0°C furnished a product



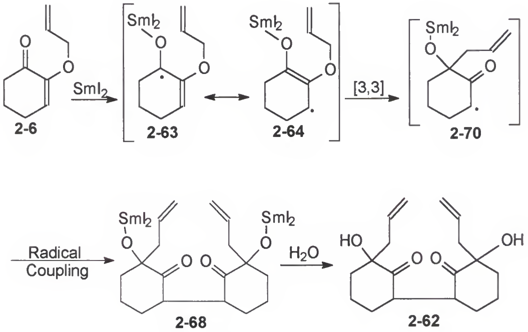
Scheme 2-21

whose proton and carbon NMRs matched very closely those of rearrangement product **2-20** (Table 1) for the tributyltin hydride mediated rearrangement. Further investigation revealed the formation of dimer product **2-62**. In order to reduce the amount of dimerization product, various hydrogen atom donors, such as tertiary butyl alcohol and methanol, were examined. Only dimerization product was isolated in all cases.



Scheme 2-22

Either radical homocoupling or an anionic coupling mechanism could account for the formation of dimerization product. Scheme 2-22 illustrates the anionic coupling mechanism, where **2-6** reacts with samarium iodide to form the samarium ketyl **2-63**, which is resonance with the samarium enolate **2-64**. Transfer of an electron to the β-radical center provides dianionic intermediate **2-65**, which then undergoes a [3,3]-sigmatropic rearrangement to furnish samarium alkoxide intermediate **2-66**. The anion α to the carbonyl can then Michael onto substrate **2-6** to give dimer **2-67**. Subsequent [3,3]-rearrangement of intermediate **2-67** and water work-up furnishes the final rearranged dimer product.



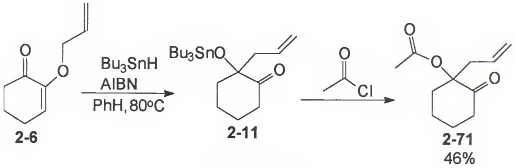
Scheme 2-23

A more straightforward and more probable radical homocoupling mechanism is outlined in Scheme 2-23. The samarium diiodide enolate is formed as before and subsequent rearrangement provides radical-anion intermediate **2-70**. A radical homocoupling occurs to provide dimer metal alkoxide intermediate **2-68**. Water work-up then furnishes the final dimerized product.

Tandem Reactions

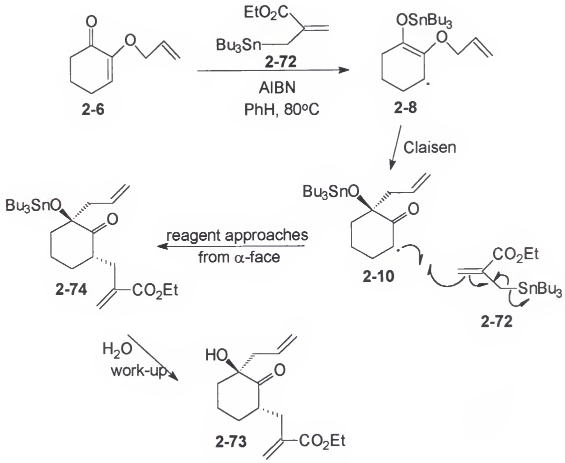
Intermediate **2-8** (Scheme 2-3) possesses two reactive centers other than the enolate carbon center. One is the oxygen tin bond; the oxygen exhibits a partially negative charge. The other is the carbon radical, which is formed β to the carbonyl. Both of these centers can be utilized to further functionalize the compound without additional purification and synthetic steps.

The reactivity of the oxygen-tributyltin bond was investigated first. The usual reaction conditions were used, except after a reaction time of three hours, 2.1 equivalents of acetyl chloride were added. This solution was stirred for an additional two hours to yield 46% of the O-acetylated product **2-71** (Scheme 2-24).



Scheme 2-24

In order to take advantage of the reactivity at the nucleophilic β-radical center, an electron deficient allyltin reagent[63] **2-72** (Scheme 2-25) was synthesized (to be addressed in Chapter 3). The 2-functionalized allyltin reagent was utilized, since the ester substituted olefin is more electrophilic and would be more likely to react with a nucleophilic radical. A much longer reaction time of 10 hrs was required, presumably due to the more difficult initiation of the substituted allyltin reagent. The reaction of 2-allyloxy-2-cyclohexenone (**2-6**) gave only one diastereomer of **2-73** in 61% yield. The relative stereochemistry present in the product most likely results from the allyltin reagent approaching on the opposite face from the tributyltin oxide group in **2-10** (Scheme 2-25), however full confirmation of the stereochemistry awaits further study.



Scheme 2-25

Conclusions

In summary, it has been demonstrated that Claisen rearrangements can be accelerated by the tandem formation of O-stannyl enolates. This unprecedented ketyl-mediated approach is as efficient as previous methods, but offers the advantage of mild conditions. Mechanistic studies support an unprecedented radical-anion intermediate for the sigmatropic rearrangement. Also, two additional reactive sites in the intermediate also offer the unique advantage of tandem functionalization.

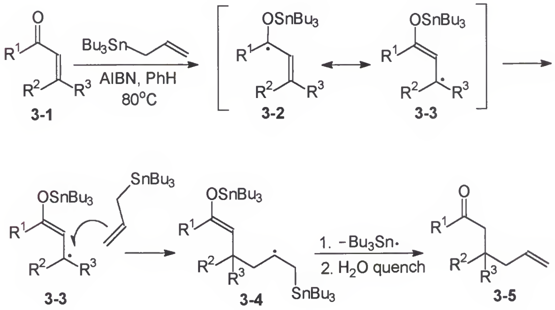
CHAPTER 3
RADICAL REACTIONS OF ENONES WITH ELECTROPHILIC ALLYLSTANNANES

Introduction

As mentioned previously, three reactive centers result from the reaction of α,β-unsaturated carbonyl substrates with tributyltin hydride. All three were investigated in Chapter 2, where the enolate carbon participated in a Claisen rearrangement, the tributyltin oxygen bond was trapped with an electrophilic reagent, and lastly the β-radical center was trapped with an electron deficient allylstannane reagent. The following paragraphs will discuss the synthesis of a suitably substituted allylstannane reagent and its application to the formation of carbon-carbon bonds from α,β-unsaturated carbonyl substrates.

One of the more commonly utilized organotin reagents in free-radical reactions as well as Lewis acid mediated reactions is allyltributylstannane.[62] New carbon-carbon bonds can be constructed from the reaction of allyltributylstannane with carbon centered radicals. In the past, allyltin reactions with phenylselenides, alkyl halides, phenylsulfides, and thiocarbonyl functions have been investigated. However, the reaction of allyltributylstannane with enones under free-radical conditions has never been investigated.

Under free radical conditions, the reaction of enone **3-1** and allylstannane should form allylic O-stannyl ketyl **3-2**, which is in resonance with O-stannyl enolate radical species **3-3**. The β-radical site should then add to the allylstannane reagent as shown in Scheme 3-1 to form radical intermediate **3-4**. Subsequent β-scission of tributyltin radical should provide, after water quenching of the enolate intermediate, allylated product **3-5** and also a molecule of tributyltin radical, which allows the free radical chain mechanism to continue. This new methodology would allow for carbon-carbon bond formation at the β-position of the enone, providing an alternative to the Michael reaction. In the Michael reaction basic organometallic conditions are required, which could epimerize chiral centers or destroy sensitive functional groups. However, this new method of β-elaboration of ketones utilizes neutral free-radical conditions,

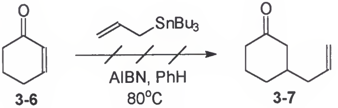


Scheme 3-1

therefore it provides we believe the only non-basic and non-nucleophilic alternative to conjugate additions of organocuprates to enones.

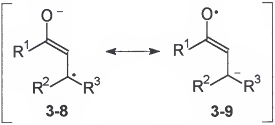
Results and Discussion

The reaction between 2-cyclohexenone (**3-6**) and allyltributylstannane with AIBN as initiator in refluxing benzene was first attempted. Twenty-four hours of refluxing gave only unreacted starting materials. Since the half-life of AIBN is only a few hours, a second reaction was conducted, where catalytic amounts of AIBN were added every 3 hours and still no product was isolated. This unsubstituted parent allylstannane reagent would simply not undergo addition to enones.



Scheme 3-2

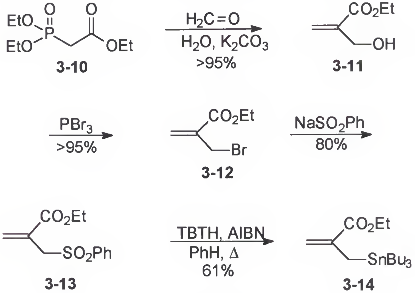
Closer examination of the electronics of the O-stannyl enolate radical intermediate **3-3** reveals two main resonance contributors (Scheme 3-3). Most alkyl radical species are inherently nucleophilic, however, the negative charge which resides at the β-position in the minor resonance contributor **3-9** enhances



Scheme 3-3

the negative character of the radical. Preliminary experimental results indicate that the radical is simply too nucleophilic to react with the electron-rich double bond of allyltributylstannane.

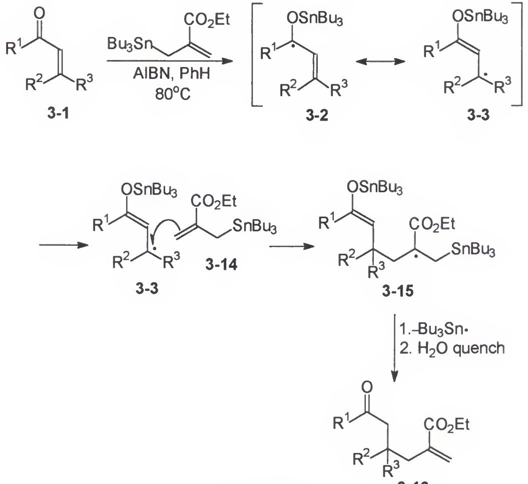
In order to take advantage of the nucleophilic character at the β-radical site, an electron deficient allylstannane reagent must be synthesized. An ester substituted allylstannane reagent was examined since a literature preparation from benzenesulfonyl precursors[63] exists. Scheme 3-4 illustrates the synthesis



Scheme 3-4

of 2-ester substituted allylstannane reagent, where triethyl phosphonoacetate (**3-10**) was reacted with an aqueous formaldehyde solution and potassium carbonate to provide the Wittig/Horner elimination product **3-11**. Hydroxymethyl acrylate was then reacted with phosphorus tribromide to afford **3-12**.[64a] In order to synthesize the final allylstannane reagent, the bromomethyl acrylate was converted to the benzenesulfonylmethyl acrylate (**3-13**) via reaction with benzenesulfinic acid-sodium salt. Reaction of **3-13** with tributyltin hydride under free radical conditions provided the desired electron deficient allyltin reagent **3-14**.[63] The last step of the synthesis presumably proceeded by the hydrostannylation across the acrylate double bond, followed by elimination of phenylsulfinyl radical.

With the electron deficient allylstannane reagent in hand, its reactivity with various types of enones was investigated. The reaction with the β-radical center was envisioned to occur as in Scheme 3-5. First a small amount of



Scheme 3-5

tributyltin radical is produced from the reaction of a catalytic amount of AIBN initiator with 2-substituted allylstannane. Tributyltin radical then reacts with the ketone to form resonance stabilized allyl O-stannyl ketyl **3-2**. The electron deficient allylstannane reagent should now react with the nucleophilic β-radical site in intermediate **3-3**. Subsequent β-scission should produce β-allylated ketone **3-16** as well as a molecule of tributyltin radical, which will continue the free-radical chain mechanism.

Various types of enones were subjected to this new methodology and the results are depicted in Tables 3-1 and 3-2.[65] The reactions required nearly 12 hours of reflux compared to only 3 or 4 hours for tributyltin hydride chemistry, presumably due to the more difficult initiation of allylstannane substrates. An additional amount of AIBN was added every 3 hours. Various substrates where treated with the electron deficient allylstannane reagent and gave allylated product in good yield (Table 3-1). The two new stereocenters present in the (-)-carvone adduct **3-26** most likely result from attack of the 2-substituted allylstannane[66] on the opposite face from the isopropenyl substituent. Axial protonation of the O-stannyl enolate results in a cis-orientation of the allyl and methyl groups. However, full confirmation of the stereochemistry awaits further investigation. The results illustrate the sensitivity of the electron-deficient allylstannane reagent; the substrates with little substitution and little steric hindrance gave product in good yield (Table 3-1). However, the more

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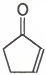
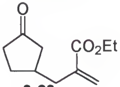
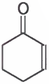
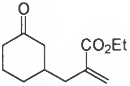
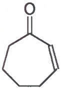
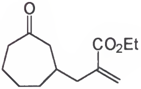
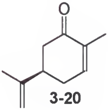
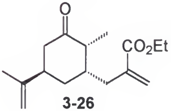
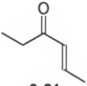
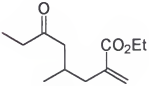
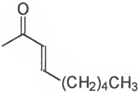
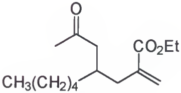
Unsaturated Ketone	Product	Yield (%)
 **3-17**	 **3-23**	58
 **3-18**	 **3-24**	61
 **3-19**	 **3-25**	67
 **3-20**	 **3-26**	61
 **3-21**	 **3-27**	65
 **3-22**	 **3-28**	63

Table 3-1

substituted or highly sterically hindered radical sites showed no reactivity (**3-29** and **3-30**,[67] shown in Table 3-2). Dimerization results from the reaction of phenyl butenone (**3-31**) with the allylstannane reagent. A long-lived resonance stabilized benzyl radical site is formed in the intermediate, therefore making dimerization more likely.

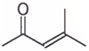
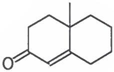
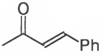
Enone	
 **3-29**	recovered st. mat.
 **3-30**	recovered st. mat.
 **3-31**	recovered dimerized pdt.

Table 3-2

Conclusions

Novel methodology for elaboration at the β site of α,β-unsaturated carbonyl substrates has been achieved. The two-substituted allylstannane reagent forms the β-radical site by reaction with enones and also acts as the radical acceptor. However, the methodology is limited; thus far, enones with 2,3-

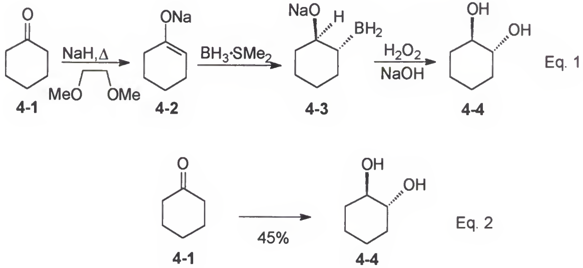
disubstituted or 2,2,3-trisubstituted olefins are the only substrates that lead to the desired β-substituted ketones. This reaction provides the only non-basic and non-nucleophilic alternative to Michael additions to enones.

CHAPTER 4

HYDROBORATION OF O-STANNYL ENOLATES: A NOVEL SYNTHESIS OF TRANS-DIOLS FROM ENONES

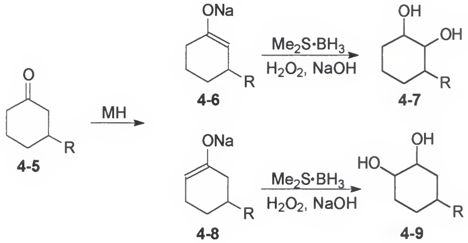
Introduction

In the past, various methods for the synthesis of trans-diols have been developed starting from alkenes, ketones, epoxides etc. However, no method has been developed for the direct one-pot formation of trans-diols from α,β-unsaturated ketones.



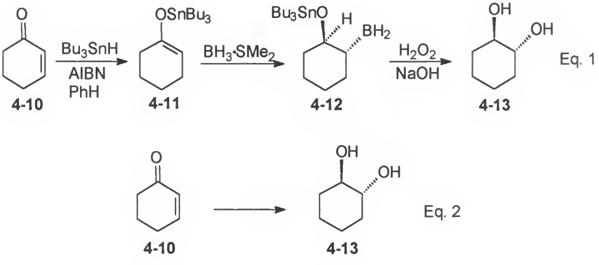
Scheme 4-1

A related reaction for saturated ketones has been studied. In the early 1970's Klein and co-workers[68] showed that hydroboration-oxidation of sodium and lithium enolates, derived from ketones, gives trans-1,2-diols in modest to low yields, as in Scheme 4-1. Substitution at the 2 position of cyclohexanone allowed the authors to prepare two different isomeric sets of trans-diols from the same starting material. This was accomplished by using different conditions to provide either the thermodynamic or kinetic enolate, which lead to different trans-diol products. However, the authors were forced to avoid 3-substituted cyclohexanones **4-5** since isomeric products would have resulted from hydroboration of two possible enolates (Scheme 4-2).

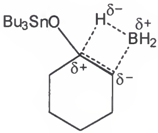


Scheme 4-2

We envisioned that O-stannyl enolates could be hydroborated and oxidized to give trans-diols as well (Scheme 4-3, eq. 1). With the recent development of a neutral-free radical method of forming O-stannyl enolates from α,β-unsaturated ketones in hand, it is possible to form the O-stannyl enolate **4-11** first, then hydroborate the enolate and oxidize to diol **4-13** in the same reaction flask. This sequence leads to an unprecedented overall transformation of an α,β-unsaturated ketone to a trans-1,2-diol functionality, placing the diol regioselectively between the ketone and olefin (Scheme 4-3, eq. 2). The hydroboration across the O-stannyl enolate occurs such that the hydride adds to the tin-oxide side of the double bond (Figure 4-4); the partially positive charge resides on the more substituted carbon and can be stabilized by the pairs of electrons on oxygen. Also, one of the advantages of using the O-stannyl



Scheme 4-3



4-14

Figure 4-1

enolate intermediate is only one enolate will form; therefore, enones with substitution at the 3-position may be used as starting substrates.

Results and Discussion

The results shown in the Table 4-1 illustrate the efficiency of this method. Hydroborations of several different cyclic enones were attempted and were

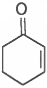
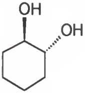
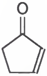
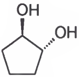
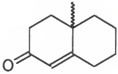
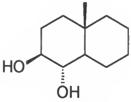
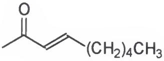
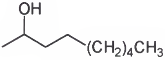
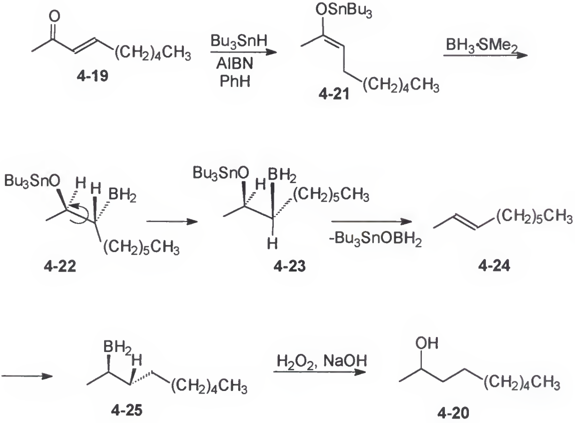
Enone	Product	Yield
 **4-10**	 **4-13**	55%
 **4-15**	 **4-16**	48%
 **4-17**	 **4-18**	56%
 **4-19**	 **4-20**	83%

Table 4-1

successful. Our investigations have found that this method is applicable to various ring systems, however when applied to acyclic systems, such as **4-19**, a mono-alcohol is isolated. This phenomenon can be explained by the formation of intermediate **4-23** (Scheme 4-4), which cannot be achieved with cyclic enones **4-10**, **4-15**, and **4-17**. Rotation affords the proper geometry for the elimination

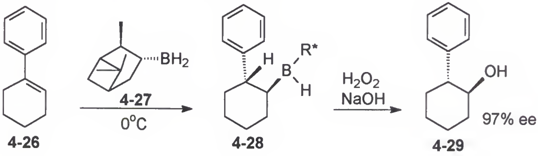


Scheme 4-4

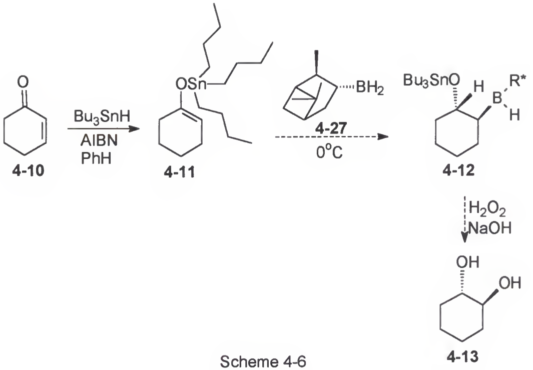
of Bu_3SnOBH_2, generating olefin **4-24**. Excess borane should hydroborate the olefin; oxidation then provides mono-alcohol **4-20**. We expected the formation of both 2-nonanol and 3-nonanol from the hydroboration of 2-nonene (**4-24**).

Brown found that hydroboration of 2-hexene leads to a 57:43 ratio of 2-hexanol and 3-hexanol.[69] It remains unclear why the regiochemistry of the hydroxyl in **4-20** is essentially all in the 2-position.

The hydroboration reaction has been studied using asymmetric induction with chiral boranes.[70] The asymmetric center can be part of the substrate undergoing hydroboration or asymmetric groups can be incorporated into the hydroborating reagent. The chiral hydroboration of cycloalkenes[71] substituted at the one position have been known to lead to good optical purity (Scheme 4-5). For instance, 1-phenylcyclohexene (**4-26**) leads to alcohol **4-29** in 97% ee when hydroborated with IpcBH$_2$ (diisopinocampheylborane, **4-27**). The next logical step is to attempt the chiral hydroboration of O-stannyl enolates using IpcBH$_2$ (Scheme 4-6). Cyclohexenone (**4-10**) was first reacted with tributyltin hydride to form the O-stannyl enolate **4-11**, which is a 1-substituted cycloalkene. Diisopinocampheylborane was then prepared and added to the solution and stirred at 0°C. Oxidation did not lead to the desired diol product. The large tributyltinoxide most likely hinders the approach of the bulky chiral borane



Scheme 4-5



Scheme 4-6

reagent. The phenyl group in **4-26** is bulky, but can align with the double bound to give a semi-planar conformer, which can be approached from the top by the bulky chiral borane reagent.

Conclusions

Conditions for the one-pot transformation of α,β-unsaturated ketones to trans-1,2-diols have been developed. An O-stannyl enolate was formed from an α,β-unsaturated ketone under neutral free-radical conditions. Hydroboration of the electron rich O-stannyl enolate double bond led to the boron intermediate. Subsequent oxidation of the boron intermediate then provided the trans-diol. Cyclic precursors work well, however acyclic precursors led to mono-alcohols.

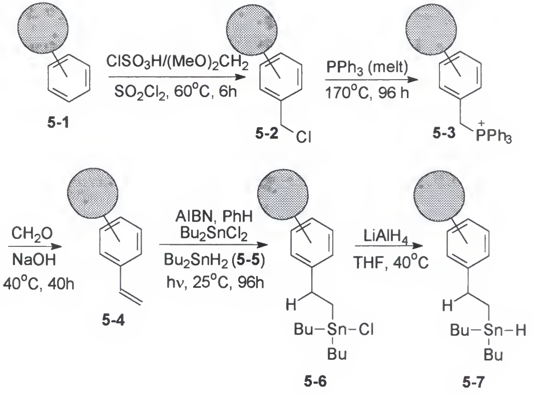
The chiral hydroboration of O-stannyl enolates was attempted; however, the reaction was not successful, apparently due to the bulk of the tributyltin oxide group.

CHAPTER 5
THE SYNTHESIS OF A POLYMER SUPPORTED ALLYLSTANNANE REAGENT

Introduction

The development of a method for the use of trialkylstannane reagents without contamination of the product with toxic stannane byproducts would be extremely useful to the pharmaceutical industry. Over the years O-stannyl byproduct separation techniques have been developed such as the DBU-I_2 technique developed by Dennis Curran (used in this dissertation).[72,73] However, none of them are entirely efficient, often requiring several separations by flash column chromatography in order obtain a pure sample. The following paragraphs outline the development of a polymer bound allylstannane reagent. In this case, simple filtration removes the stannane reagent and stannane biproducts from the desired product. This methodology also offers the option of regeneration of the reagent.

The origin of this work was the development of two polymer bound organotin hydride reagents.[74] The first reagent was synthesized by mono-hydrostannylation m-/p-divinylbenzene, polymerization, and reduction to the polymer bound tin-hydride with dibutylaluminum hydride. A slightly different approach was taken for the synthesis of the second reagent (Scheme 5-1). More recently, Pereyre and co-workers[75] attached tin hydride to Amberlite XE

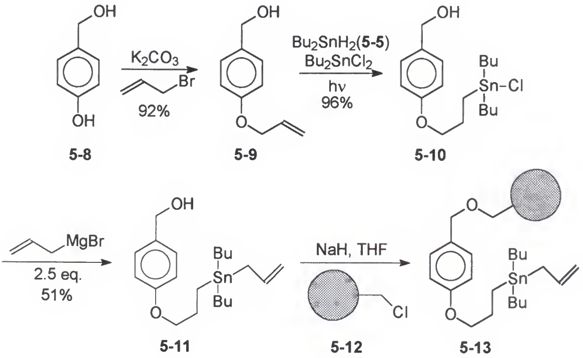


Scheme 5-1

305. However, tin pollution occurred as a result of abrasion of the bead surface by mechanical stirring. Also, reactions on a crosslinked polymer support require much longer reaction times than reactions in solution phase.

Results and Discussion

The first approach to the synthesis of our polymer bound allylstannane reagent involved the solution phase synthesis of allylstannane attached to a linker, then subsequent attachment to the insoluble crosslinked polymer support. This allowed the characterization of products and determination of yield for each step. Scheme 5-2 illustrates the synthetic route, where 4-hydroxybenzyl alcohol was chosen as a linker to add weight and to allow for the facile removal of the reagent at the end of the route for the percent loading calculation. First, the most acidic proton (the phenolic proton) was replaced with an allyl group. Hydrostannylation with Bu_2SnHCl and the olefin in **5-9** provided stannyl-chloride substrate **5-10**. Reaction with allyl magnesium bromide gave the allylstannane reagent attached to the linker. The final step of the route involves the



Scheme 5-2

deprotonation of alcohol **5-11** and displacement of the chloride anion from Merrifield resin **5-12** (insoluble chloromethyl polystyrene bead). The reaction could not be monitored by traditional methods, such as NMR, TLC, GC etc. Therefore, hydrogen and palladium on carbon was used to remove the reagent

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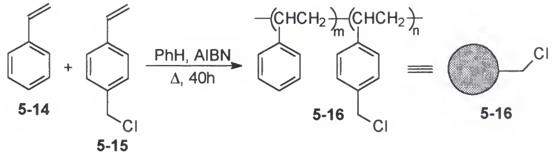
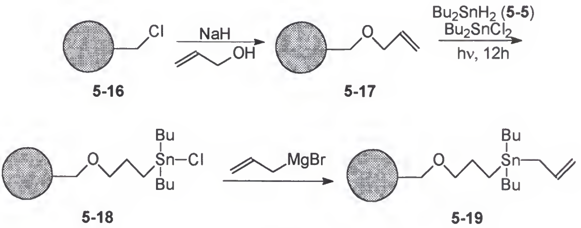
and linker from the polymer in order to calculate percent loading. Various methods of attaching the linker and reagent to the polymer were attempted, including NaH/THF and NaH/DMF. In each case after hydrogenolysis, none of the reagent was isolated. Examination of the literature revealed that harsh conditions[76] are required for ether synthesis on a crosslinked polymer support, such as Merrifield resin.

A non-crosslinked polystyrene polymer support was developed in 1970's for protein synthesis. Researchers found that the rate of coupling reactions for the soluble non-crosslinked polymer is of the same order of magnitude as classical liquid phase peptide synthesis, translating to a rate 100 times faster than insoluble solid phase reactions.[77] Other merits of the non-crosslinked polystyrene (NCPS) polymer include: (1) NCPS is inexpensive to prepare; (2) NCPS is soluble in commonly used organic solvents (EtOAc, benzene, $CHCl_3$, CH_2Cl_2 and THF), however, NCPS is insoluble in MeOH and water allowing for easy purification of reaction intermediates; (3) polymer bound substrates can be analyzed by NMR spectroscopy without cleavage from polymer support; (4) the amount of polymer loading can be controlled; [78] (5) as mentioned earlier, reactions on this soluble polymer support occur at a rate up to 100 times faster than insoluble supports. Also, the mechanical abrasion of the insoluble polymer bound stannane reagent (resulting in tin pollution) should be avoided when a soluble non-crosslinked polymer is applied.



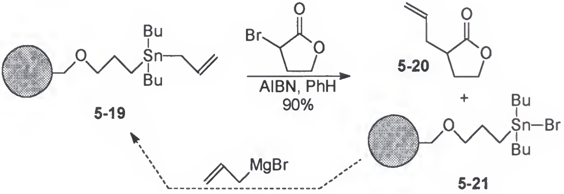
Scheme 5-3

With the ability to the monitor every step of the reaction, a new route involving the soluble non-crosslinked polystyrene polymer support was investigated. Non-crosslinked polystyrene with 0.3 mmol Cl-CH_2/g was synthesized, as in Scheme 5-3. The chloromethyl polystyrene **5-16** was then reacted with allyl alcohol, NaH, and dimethylacetamide to give polymer bound



Scheme 5-4

allyl **5-17** (Scheme 5-4). The product was isolated by simply pouring the reaction mixture into cold methanol (-78°C), filtering and washing the white solid with methanol. Analysis of the central region of the ^1H NMR (2.5-6.2 ppm) revealed the presence of an allyl group. Hydrostannylation of the olefin with Bu_2SnHCl then provided stannyl-chloride substrate **5-18**, evidenced by the disappearance of the olefin peaks in ^{1}H NMR. Subsequent reaction with allylmagnesium bromide provided the polymer bound allylstannane reagent. Reaction of reagent **5-19** with α-bromo-butyrolactone gave α-allyl-butyrolactone (**5-20**) with little tin contamination. Investigations with various alkylhalides must be undertaken in order to realize the true scope of this soluble polymer supported allyltin reagent. The recycling capabilities of the substrate must also be investigated (Scheme 5-5). Polymer bound tin-halide **5-21** is produced during the reaction of **5-19** with alkylhalide and should easily revert back to allyltin upon reaction with allylmagnesium bromide.



Scheme 5-5

Conclusions

The synthesis of a non-crosslinked polymer linked allylstannane reagent was investigated. Once reactions with various alkyl halides are investigated, this novel new reagent should have numerous advantages over the crosslinked polymer bound tin-hydride counterparts, including less tin pollution and faster reaction times.

CHAPTER 6
EXPERIMENTAL

General Methods

Proton nuclear magnetic resonance (^1H NMR) spectra were recorded on a Varian Gemini-300 (300 MHz) spectrometer. Carbon 13 spectra were recorded on a Varian Gemini-300 spectrometer at 75 MHz. Chemical shifts are reported in ppm down field relative to tetramethyl silane as an internal standard in $CDCl_3$. All reactions were run under an inert atmosphere of argon using an oven dried apparatus. All yields reported refer to isolated material judged to be homogeneous by thin layer chromatography (TLC) and NMR spectroscopy. Solvents were dried according to established procedures by distillation under inert atmosphere from appropriate drying agents. Analytical TLC was performed using Aldrich Z12272-6 precoated silica plates (0.25 mm) visualizing with UV light (254 nm) or p-anisaldehyde in ethanol with acetic acid as an indicator. Column chromatography was performed using Kieselgel silica gel 60 (230-400 mesh) by standard flash chromatography techniques. GC experiments were performed on a Varian 3500 capillary gas chromatograph using J & W fused silica capillary column (DB5-30W; film thickness 0.25).

Experimental Procedures

2-allyloxy-2-cyclohexenone (2-6).[52]

The following experimental procedure is identical to that reported by Poneras.[57] Cyclohexanedione (1.0 g, 8.9 mmol), allyl bromide (1.6 mL, 18.7 mmol) and potassium carbonate (2.6 g, 18.7 mmol) were combined in a 50 mL round bottom flask with reagent grade acetone (18 mL). The mixture was heated to reflux overnight (monitored by TLC), then poured over water and extracted with ether (3 X 50 mL). The organic phase was then dried with sodium sulfate, concentrated under reduced pressure, and subjected to column chromatography to yield the enol ether **2-6** (440 mg, 33% yield). **2-6** is identical in all respects to that of Ikeda and co-workers.[52] ^{1}H NMR δ 6.0 (complex m, 2H), 5.4 (d of d, J=1.2, 17.4, 1H), 5.3 (d of d, J=1.2, 10.2, 1H), 4.3 (d, J=5.7, 2H), 2.5 (t, J=7.5, 2H), 2.4 (q, J=10.5, 2H), 2.0 (p, J=6.3, 2H); ^{13}C NMR δ 194.1, 150.0, 132.7, 118.4, 117.7, 68.4, 38.6, 24.2, 22.7.

2-allyloxy-3,5,5-trimethyl-2-cyclohexenone (2-16).[57]

The following procedure and characterization is identical to that reported by Ponaras.[57] 3,5,5-Trimethyl-1,2-cyclohexanedione (**2-36**) (2.0 g, 13 mmol), allyl bromide (2.36 mL, 27.2 mmol), potassium carbonate (3.8 g, 27.2 mmol), and reagent grade acetone (26 mL) combined in a 100 mL flask and heated to reflux (24 h). Reaction was poured over water and extracted with ether (3 X 50 mL).

The organic phase was dried with sodium sulfate, concentrated under reduced pressure, and subjected to flash column chromatography to yield enol ether **2-16** (2.04 g, 81%). ^{1}H NMR δ 5.9 (m, 1H), 5.1 (m, 2H), 4.3 (m, 2H), 2.2 (s, 2H), 2.1 (s, 2H), 1.8 (s, 3H), 1.0 (s, 6H); ^{13}C NMR δ 194.4, 146.8, 143.1, 134.3, 117.7, 72.6, 52.1, 45.4, 32.9, 28.0, 17.9.

2-allyloxy-3-ethyl-2-cyclopentenone (2-17).

The following procedure is identical to that reported by Poneras.[57] 3-ethyl-1,2-cyclopentanedione (1.0g, 7.93 mmol), allyl bromide (1.44 mL, 16.7 mmol), K_2CO_3 (2.3g, 16.7 mmol) and acetone (15.9 mL) were combined and heated to reflux under argon. The starting material was consumed after 6h (monitored by TLC). The reaction mixture was poured into water (20 mL) and extracted with ether (3 X 20 mL). The organic phases were combined and washed with brine and dried with Na_2SO_4. The solvent was removed under reduced pressure to afford O-allylated product (judged to be pure by TLC and NMR, 1.24 g, 94%). Rf=0.54 (35:65 EtOAc:Hex). ^{1}H NMR δ 5.9 (m, 1H), 5.3 (d of d, J=1.2, 17.4 Hz, 1H), 5.2 (d of d, J=1.2, 10.2 Hz, 1H), 4.6 (d, J=5.7 Hz, 2H), 2.5-2.3 (complex m, 6H), 1.1 (t, J=7.5 Hz, 3H); ^{13}C NMR δ 203.6, 160.8, 150.7, 134.1, 117.6, 70.8, 32.9, 24.5, 22.0, 11.4; IR (neat oil) 3084, 2978, 1719, 1631, 1461, 1384, 1190 cm^{-1}; mass spectrum (EI) 166.1 (71.8), 137.1 (38.5), 110.1 (19.2), 109.1 (17.2); exact mass (EI) for $C_{10}H_{14}O_2$ calcd. 166.0994, found 166.0981.

1-phenyl-2-allyloxy-2-propen-1-one (2-18).

The following procedure is identical to that reported by Harmon and Hutch.[60] Amine **2-48** (9.87 g, 36.2 mmol) and MeI (33.8 mL, 54.2 mmol) were combined in methanol (52 mL). The flask was covered with aluminum foil and the solution was allowed to sit overnight. The solvent was removed under reduced pressure, and the resulting oil was treated with $NaHCO_3$ (sat. soln., 200mL). The aqueous phase was extracted with CH_2Cl_2 (3 X 100 mL) and the organic phase was dried with sodium sulfate. The solvent was removed under reduced pressure to yield a yellow oil (3.2 g, 47%), which was used in the next step without further purification. Rf=0.71 (35:65 EtOAc:Hex). ^1H NMR δ 7.8 (d, J=7.2 Hz, 2H), 7.5 (complex m, 3H), 6.0 (m, 1H), 5.3 (d of d, J=1.2, 17.1 Hz, 1H), 5.2 (d of d, J=1.2, 10.5 Hz, 1H), 5.0 (d, J=3.0 Hz, 1H), 4.7 (d, J=2.7 Hz, 1H), 4.4 (d, J=5.1 Hz, 2H), ^{13}C NMR δ 191.3, 157.6, 136.6, 132.6, 132.2, 129.8, 128.0, 118.0, 95.6, 69.1, IR (neat oil) 3061, 2931, 2871, 1674, 1444 cm^{-1}; mass spectrum (CI) 189.1 (100), 171.0 (3.9), 145.1 (6.1),143.1 (5.4), 105.0 (45.6); exact mass (CI) for $C_{12}H_{13}O_2$ (M+1) calcd. 189.0916, found 189.0947.

2-(2-nonynoxy)-2-cyclohexenone (2-19).

Cyclohexanedione (1.00 g, 8.9 mmol), 2-nonyn-1-ol (1.25 g, 8.9 mmol), p-toluenesulfonic acid (34 mg, 0.018 mmol), and benzene (45 mL) were combined

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in a 100 mL round bottom flask, equipped with a Dean-Stark tube and condenser. The reaction was heated to reflux overnight. A saturated solution of K_2CO_3 was added to the cooled reaction mixture. The solution was extracted with ether (3 X 50 mL), and the organic phases were combined and dried with Na_2SO_4. The solution was then concentrated under reduced pressure and subjected to column chromatography to provide enol ether **2-19** (1.01 g, 49%). Rf=0.51 (35:65 EtOAc:Hex). ^{1}H NMR δ 5.9 (t, J=4.8 Hz, 1H), 3.8 (t, J=7.5 Hz, 2H), 2.6 (m, 2H), 2.5 (t, J=6.3 Hz, 2H), 2.4 (m, 2H), 2.1 (m, 2H), 2.0 (m, 2H), 1.5 (m, 2H), 1.3 (m, 4H), 0.9 (t, J=6.9 Hz, 3H); ^{13}C NMR δ 194.2, 150.4, 118.3, 82.2, 75.3, 66.3, 38.8, 31.0, 28.5, 24.4, 22.8, 22.1, 19.3, 18.6, 13.9. IR (neat oil) 3060, 2931, 2861, 1731, 1690, 1625, 1367 cm-1; mass spectrum (EI) 234.2 (17.1), 177.1 (23.7), 152.1 (25.3), 125.1 (100), 93.1 (40.8), 79.0 (46.9), 67.1 (87.8), 41.0 (59.7); exact mass (EI) for $C_{15}H_{22}O_2$ calcd. 234.1620, found 234.1606.

2-allyl-2-hydroxycyclohexanone (2-20).[79]

2-allyloxy-2-cyclohexanone (190 mg, 1.25 mmol), tributyltin hydride (0.37 mL, 1.38 mmol), and AIBN (41mg, 0.25 mmol) were dissolved in benzene (2.5 mL) and degassed for 20 min with a stream of argon. The reaction mixture was then heated to reflux (3 h, monitored by TLC). The reaction was allowed to cool and was diluted with ether (10 mL). DBU (0.21 mL, 1.4 mmol) and 3-4 drops of water were added to the stirring solution. An ethereal solution of iodine was added dropwise until the iodine color persisted. The mixture was then filtered rapidly through silica gel with ether. The filtrate was then concentrated under reduced pressure and subjected to flash column chromatrography to yield the Claisen rearrangement product (142 mg, 74%). Spectral data for alcohol **2-20** is identical in all respects to that reported by Mutai and co-workers.[79] ^{1}H NMR δ 5.7 (m, 1H), 5.1 (m, 2H), 4.0 (s, OH), 2.6-2.4 (complex m, 4H), 2.2 (d of d, J=2.4, 12.6 Hz, 1H), 2.1 (m, 1H), 1.8-1.5 (complex m, 4H); ^{13}C NMR δ 213.4, 131.6, 118.7, 78.7, 41.7, 40.2, 38.2, 27.7, 22.5.

2-allyl-2-hydroxy-4,6,6-trimethylcyclohexanone (2-21).

2-allyloxy-3,5,5-trimethyl-2-cyclohexenone (400mg, 2.06 mmol), tributyltin hydride (0.61 mL, 2.27 mmol), and AIBN (67.6 mg, 0.41 mmol) were dissolved in benzene (4.1 mL) and degassed for 20 min with a stream of argon. The reaction mixture was then heated to reflux (3h, monitored by TLC). The reaction was allowed to cool and was diluted with ether (20 mL). DBU (0.34 mL, 2.28 mmol), and 3-4 drops of water were added to the stirring solution. An ethereal solution of iodine was added dropwise until the iodine color persisted. The mixture was then filtered rapidly through silica gel with ether. The filtrate was concentrated under reduced pressure and subjected to flash column chromatography to yield the Claisen rearrangement product (250 mg, 62%). Rf=0.68 (35:65 EtOAc:Hex) ^{1}H NMR δ 5.8-5.6 (m, 1H), 5.1 (complex m, 2H), 4.0 (s, OH), 2.8 (m, 1H), 2.5 (complex m, 2H), 2.1 (d of d, J=3.3, 14.4 Hz, 1H), 1.8

(m, 1H), 1.7 (m, 1H), 1.4 (m, 1H), 1.3 (s, 3H), 1.2 (d, J=7.0 Hz, 3H), 1.0 (s, 3H); ^{13}C NMR δ 216.1, 132.4, 118.7, 77.6, 52.8, 49.6, 44.2, 37.3, 33.1, 30.8, 27.2, 14.3; IR (neat oil) 3473, 3071, 2959, 1713, 1677, 1460, 1378, 1181, 992 cm^{-1}; mass spectrum (CI) 197.1 (100), 179.1 (82.9); exact mass (CI) for $C_{12}H_{21}O_2$ (M+1) calcd 197.1542, found 197.1576.

2-allyl-5-ethyl-2-hydroxycyclopentanone (2-22).

2-allyloxy-3-ethyl-2-cyclohexenone (270 mg, 1.63 mmol), tributyltin hydride (1.5 mL, 5.61 mmol), and AIBN (168 mg, 0.98 mmol) were dissolved in benzene (2.5 mL) and degassed for 20 min with a stream of argon. The reaction mixture was then held at reflux for 3h (monitored by TLC). The reaction was allowed to cool and was diluted with ether (10 mL). DBU (0.84 mL, 5.61 mmol) and 3-4 drops of water were added to the stirring solution. An ethereal solution of iodine was added dropwise until the iodine color persisted. The mixture was then filtered rapidly through silica gel with ether. The filtrate was then concentrated under reduced pressure and subjected to flash column chromatography to yield the Claisen rearrangement product (169 mg, 62%). Rf=0.53 (35:65 EtOAc:Hex). ^{1}H NMR δ 5.7 (m, 1H), 5.1 (complex m, 2H), 2.4-2.1 (complex m, 3H), 2.0 (complex m, 1H), 1.9 (complex m, 1H), 1.8 (s, OH), 1.7 (complex m, 1H), 1.4 (m, 1H), 1.2 (m, 2H), 0.9 (t, J=7.2 Hz, 3H); ^{13}C NMR δ 219.8, 132.0, 119.5, 78.4, 47.9, 41.4, 32.9, 23.8, 23.5, 11.7; IR (neat oil) 3397, 3089, 2968, 1739, 1267, 1048, 739 cm^{-1}; mass spectrum (CI) 169.1 (39.4), 151.1 (100), 123.1 (17.5); exact mass (CI) for $C_{10}H_{17}O_2$ (M+1) calcd. 169.1229, found 169.1231.

3-hydroxy-3-phenyl-5-hexene-2-one (2-23).[50]

1-phenyl-2-allyloxy-2-propen-1-one (170 mg, 1.06 mmol), tributyltin hydride (0.27 mL, 1.17mmol), and AIBN (18 mg, 0.21 mmol) were dissolved in benzene (1.8 mL) and degassed for 20 min with a stream of argon. The reaction mixture was then held at reflux for 6h (monitored by TLC). The reaction was allowed to cool and was diluted with 20mL of ether. DBU (0.34 mL, 2.28 mmol), and 3-4 drops of water were added to the stirring solution. An ethereal solution of iodine was added dropwise until the iodine color persisted. The mixture was then filtered rapidly through silica gel with ether. The resulting filtrate was then concentrated under reduced pressure and subjected to flash column chromatography to yield the Claisen rearrangement product (87 mg, 51%). Substrate **2-23** is identical in all respects to that of Koreeda and Luengo.[50] Rf=0.56 (35:65 EtOAc:Hex). ^{1}H NMR δ 7.5-7.2 (complex m, 5H), 5.7 (m, 1H), 5.2 (m, 2H), 4.2 (s, OH), 2.9 (m, 2H), 2.1 (s, 3H); ^{13}C NMR δ 208.7, 140.4, 132.1, 128.7, 128.0, 125.9, 119.6, 82.1, 41.4, 24.0.

2-(2-nonynoxy)-cyclohexanone (2-24).

2-(2-nonynoxy)-2-cyclohexenone (150mg, 0.64 mmol), tributyltin hydride (0.19 mL, 0.7 mmol), and AIBN (21 mg, 0.31 mmol) were dissolved in benzene

(1.3 mL) and degassed for 20 min with a stream of argon. The reaction mixture was then held at reflux until no further progress had been made (3h, monitored by TLC). The reaction was allowed to cool and was diluted with 10mL of ether. DBU (0.13 mL, 0.9 mmol), and 3-4 drops of water were added to the stirring solution. An ethereal solution of iodine was added dropwise until the iodine color persisted. The mixture was then filtered rapidly through silica gel with ether. The filtrate was then concentrated under reduced pressure and subjected to flash column chromatography to yield the reduced product (105 mg, 70%). Rf=0.57 (35:65 EtOAc:Hex). ^{1}H NMR δ 3.9 (q, J=5.4 Hz, 1H), 3.7 (q, J=7.5 Hz, 1H), 3.5 (q, J=7.5 Hz, 1H), 2.6-2.4 (complex m, 3H), 2.3-2.1 (complex m, 4H), 1.9 (m, 2H), 1.8-1.6 (complex m, 3H), 1.5 (complex m, 2H), 1.4-1.2 (complex m, 4H), 0.9 (t, J=6.9 Hz, 3H); ^{13}C NMR δ 210.1, 83.0, 81.8, 76.4, 68.8, 40.5, 34.4, 31.0, 28.6, 27.6, 23.0, 22.2, 20.3, 18.7, 14.0. IR (neat oil) 2926, 2859, 1722, 1453, 1113 cm^{-1}; mass spectrum (EI) 237.2 (1.0), 127.1 (40.5), 115.1 (32.1), 97.0 (28.0), 69.1 (100), 67.1 (28.8); exact mass (EI) for $C_{15}H_{25}O_2$ (M+1) calcd. 237.1855, found 237.1814.

3,5,5-trimethyl-2,3-epoxycyclohexanone (2-35).[55]

The following procedure and characterization is identical in all respects to that of Salladie and Hutt.[55] Isophorone (2.0 g, 14.5 mmol), 30% H_2O_2 (3.0 mL, 29 mmol), methanol (26 mL), and H_2O were combined in a 100mL round bottom flask and cooled to 0°C in an ice water bath. Potassium carbonate (sat. soln.,

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0.2 mL) added dropwise resulting in a milky white solution. The mixture was stirred at room temperature overnight (monitored by TLC) to give a clear colorless solution, which was extracted with ether (3 X 50 mL). The organic phase was then dried with sodium sulfate and concentrated under reduced pressure to yield isophorone oxide (deemed pure by NMR and G. C., 2.23 g, 99%). ^{1}H NMR δ 3.1 (s, 1H), 2.8 (s, 1H), 2.7 (s, 1H), 2.1 (s, 1H), 2.0 (s, 1H), 1.9-1.7 (m, 2H), 1.4 (s, 3H), 1.0 (s, 3H), 0.9 (s, 3H); ^{13}C NMR δ 207.8, 64.2, 61.4, 48.0, 42.8, 36.0, 30.8, 27.9, 24.0.

3,5,5-trimethyl-1,2-cyclohexanedione (2-36).[56]

The following procedure and characterization of **2-36** is identical in all respects to that of Payne.[56] Isophorone oxide (2.1 g, 13.6 mmol) was added dropwise to a 0°C solution of concentrated hydrochloric acid (9 mL). The remaining substrate was rinsed into 0°C reaction with cold hydrochloric acid (1 mL). After 16 hours of stirring the brown mixture was then diluted with H_20 (20 mL) and filtered through a Buckner funnel to give a brown solid, which was recrystallized from hexanes to give the dione (white crystalline, 839 mg, 40%). M.P.=85-87°C, Lit M.P.= 91-92°C. ^{1}H NMR δ 6.1 (s, 1H), 2.4 (s, 2H), 2.3 (s, 2H), 1.9 (s, 3H), 1.1 (s, 6H); ^{13}C NMR δ 194.0, 143.1, 126.8, 49.3, 44.7, 33.5, 28.4, 17.1.

1-phenyl-2-allyloxy-ethanol (2-43).[80]

The following procedure and characterization of alcohol **2-43** is identical in all respects to that of Swern and co-workers.[80] Sodium metal (115 mg, 5.0 mmol) was carefully combined with allyl alcohol (11.3 mL, 166 mmol) while cooling in an ice water bath. The ice water bath was removed and the allyl alcohol solution was stirred at room temperature for 20 min. Styrene oxide (2.0 g, 16.6 mmol) was then added dropwise over 5 minutes and the mixture was stirred at room temperature for 1 hour then heated to reflux for 1 hour. The mixture was then quenched with just enough H_2SO_4 to make the solution nuetral. Ether (40 mL) was added and the organic phase was washed with H_2O (2 X 40 mL), then the aqueous phase was back extracted with ether (3 X 30 mL). The organic phase was dried with sodium sulfate, concentrated under reduced pressure, and subjected to flash column chromatography to yield alcohol **2-43** (2.9 g, 98%). ^{1}H NMR δ 7.3 (m, 5H), 5.9 (m, 1H), 5.2 (m, 2H), 4.9 (m, 1H), 4.0 (d, J=13.3, 2H), 3.5 (m, 2H), 3.1 (s, OH).

1-phenyl-2-allyloxy-ethanone (2-44).

The following procedure is identical to that developed by Swern and co-workers.[58] Freshly distilled oxalyl chloride (7.8 mL, 91.5 mmol) and freshly distilled CH_2Cl_2 (270 mL) were combined under argon and cooled to -78°C. Dimethyl sulfoxide (6.5 mL, 91.5 mmol) and CH_2Cl_2 (50 mL) were combined and added dropwise to the oxalyl chloride solution, so as to keep the temperature of the solution below -60°C. 1-phenyl-2-allyloxy-ethanol (7.4 g, 41.6 mmol) and CH_2Cl_2 (50 mL) were combined and added dropwise to the cooled solution. The solution was allowed to stir for fifteen minutes, after which the triethylamine (27.6 g, 208 mmol) was added dropwise. The solution was then allowed to warm to room temperature. Ether (100 mL) and water (100 mL) were added to the solution. The layers were separated and the water layer was washed with ether (3 X 50 mL). The organic phases were combined and dried with sodium sulfate. The solvent was then removed under reduced pressure, and the resulting oil was used in the next step without further purification. Rf=0.59 (35:65 EtOAc:Hex). ^{1}H NMR δ 7.9 (d, J=8.1 Hz, 2H), 7.5 (complex m, 3H), 6.0 (m, 1H), 5.3 (d of q, J=1.8, 17.4 Hz, 1H), 5.2 (d of q, J=1.8, 10.5 Hz, 1H), 4.8 (s, 2H), 4.2 (d of t, J=1.5, 6 Hz, 2H); ^{13}C NMR δ 196.2, 134.9, 133.9, 133.4, 128.6, 127.8, 118.0, 72.5, 72.3. IR (neat oil) 3072, 2919, 2872, 1696, 1599, 1448 cm^{-1}; mass spectrum (EI) 177.1 (16.1), 120.1 (54.8), 105.0 (100), 77.0 (37.5), 69.0 (21.6); exact mass (EI) for $C_{11}H_{13}O_2$ (M+1) calcd. 177.0916, found 177.0935.

Amine 2-48.

The following procedure is identical to that developed by Ohno and co-workers.[59] 1-phenyl-2-allyloxy-ethanone (7.3 g, 41.6 mmol), dioxolane (11.6 mL, 166.4 mmol), concentrated hydrochloric acid (0.17 mL, 2.08 mmol), and piperidine hydrochloride (6.22 g, 51.17 mmol) were combined in a round bottom flask equipped with a condenser. The solution was placed in a 90°C oil bath and held at reflux for 7h. H_2O (25 mL) was added along with ethyl acetate (50 mL). The layers were separated and the aqueous phase was extracted with ethyl acetate (3 X 50 mL). The organic phase was dried with sodium sulfate and the solvent was removed under reduced pressure. The crude oil was subjected to flash column chromatography to yield **2-48** (9.87 g, 89%). ^{1}H NMR δ 8.1 (d, J=6.6 Hz, 2H), 7.5 (complex m, 3H), 5.9 (m, 1H), 5.3 (d of d, J=1.8, 17.4 Hz, 1H), 5.2 (d of d, J=1.2, 10.2 Hz, 1H), 4.8 (m, 1H), 4.1 (d of d, J=6.0, 13.0 Hz, 1H), 4.0 (d of d, J=6.0, 13.0 Hz, 1H), 2.8 (m, 2H), 2.4 (m, 4H), 1.6-1.3 (complex m, 6H); ^{13}C NMR δ 200.1, 135.8, 134.3, 133.0, 128.7, 128.4, 117.6, 81.1, 71.1, 61.4, 54.9, 25.9, 24.1. IR (neat oil) 3072, 2928, 2852, 1685, 1446, 1098 cm^{-1}. mass spectrum (EI) 274.2 (1.8), 105.0 (15.3), 98.1 (100); exact mass (EI) for $C_{17}H_{24}NO_2$ (M+1) calcd. 274.1807, found 274.1797.

2-propoxy-2-cyclohexenone (2-53).

Cyclohexanedione (1.0 g, 8.92 mmol), n-propyl alcohol (0.64 g, 10.7 mmol), p-toluenesulfonic acid (34 mg, 0.02 mmol), and benzene (45 mL) were combined in a round bottom flask equipped with a Dean-Stark tube and condenser. The reaction was heated to reflux overnight. A saturated solution of K_2CO_3 (20 mL) was added to the cooled reaction mixture, and the solution was extracted with ether (3 X 40 mL). The organic phases were combined and dried with Na_2SO_4. The solvent was then removed under reduced pressure. The crude oil was then subjected to column chromatography to yield the enol ether (1.24 g, 90% yield). Rf=0.42 (35:65 EtOAc:Hex). ^{1}H NMR δ 5.9 (t, J=4.5 Hz, 1H), 3.6 (t, J=6.9 Hz, 2H), 2.5 (t, J=6.6 Hz, 2H), 2.4 (q, J=5.7 Hz, 2H), 2.0 (m, 2H), 1.8 (m, 2H), 1.0 (t, J=7.5 Hz, 3H); ^{13}C NMR δ 194.3, 150.8, 117.2, 69.1, 38.8, 24.5, 22.9, 22.0, 15.3. IR (neat oil) 3069, 2955, 2872, 1731, 1690, 1619, 1261 cm-1; mass spectrum (EI) 154.1 (62.2), 96.1 (58.0), 84.0 (69.2), 70.0 (100), 41.0 (78.0); exact mass (EI) for $C_9H_{14}O_2$ calcd. 154.0994, found 154.0985.

2-propoxycyclohexanone (2-54).

2-Propoxy-2-cyclohexenone (200 mg, 1.3 mmol), Pd/C (cat. amnt.), and ethyl acetate (2.6 mL) were combined in a round bottom flask under argon. A T-joint fitted with a hydrogen filled balloon was attached to the round bottom flask. The round bottom flask was evacuated with an aspirator, then filled with hydrogen from the balloon. Evacuating and purging with hydrogen was repeated twice to insure an air-free environment inside the round bottom flask. The solution was stirred vigorously for 30 min., and the carbon was removed by filtration. The solvent was removed under reduced pressure and the crude oil was subjected to column chromatography to yield **2-54** (186 mg, 92%). Rf=0.55 (35:65 EtOAc:Hex). ^{1}H NMR δ 3.8 (q, J=5.4 Hz, 1H), 3.5 (q, J=7.5 Hz, 1H), 3.3 (q, J=7.5 Hz, 1H), 2.5 (m, 1H), 2.3-2.1 (complex m, 2H), 1.9 (m, 2H), 1.8-1.5 (complex m, 5H), 0.9 (t, J=7.5 Hz, 3H); ^{13}C NMR δ 210.5, 82.7, 71.7, 40.3, 34.4, 27.6, 22.9, 22.8, 10.3. mass spectrum (CI) 157.1 (M+1, 32.3), 155.0 (100), 113.1 (51.9); exact mass (CI) (M+1) for $C_9H_{17}O_2$ calcd. 157.1229, found 157.0935.

2-(2-propenoxy)cyclohexanol (2-56).[81]

Allyl alcohol (5.92 g, 102 mmol), and Na metal (70 mg, 30.1 mmol) were combined under argon while cooling in an ice-water bath. After stirring for 10 min., cyclohexaneoxide (1.0 g, 10.2 mmol) was added dropwise over a period of 10 min. The ice-water bath was removed, and the solution was stirred at room temperature for 30 min. The solution was heated to reflux for 1 hour, then cooled and quenched with H_2SO_4 (0.75 M) until just neutral. The solution was diluted with ether (30 mL) and washed twice with H_2O (10 mL). The combined aqueous layers were then washed twice with ether (20 mL), and the organic phases were combined and dried with Na_2SO_4. The solution was concentrated under reduced pressure to yield **2-56** (pure by G.C., 1.32 g, 83%). Alcohol **2-56** is identical in all respects to that of Salomon and co-workers.[81] Rf=0.27 (35:65 EtOAc:Hex). ^1H NMR δ 6.0 (m, 1H), 5.3 (d of d, J=1.8, 17.4 Hz, 1H), 5.2 (d of d, J=1.2, 10.2 Hz, 1H), 4.2 (d of d, J=5.4, 12.6 Hz, 1H), 4.0 (d of d, J=5.7, 12.6 Hz, 1H), 3.5 (m, 1H), 3.1 (m, 1H), 2.7 (s, OH), 2.0 (complex m, 2H), 1.7 (m, 2H), 1.3 (m, 4H), ^{13}C NMR δ 135.1, 116.9, 83.2, 73.7, 69.7, 32.0, 29.2, 24.2, 23.9.

2-(2-propenoxy)cyclohexanone (2-57). [81]

The following procedure is identical to that developed by Swern and co-workers.[80] Freshly distilled oxalyl chloride (0.53 mL, 6.2 mmol) and freshly distilled CH_2Cl_2 (5 mL) were combined under argon and cooled to -78°C. Dimethyl sulfoxide (0.44 mL, 6.2 mmol) and CH_2Cl_2 (3 mL) were combined and added dropwise to the oxalyl chloride solution, so as to keep the temperature of the solution below –60°C. 2-(2-propenoxy)cyclohexanol (440 mg, 2.8 mmol) and CH_2Cl_2 (3 mL) were combined and added dropwise to the –78°C solution. The solution was allowed to stir for fifteen minutes, after which the triethylamine (1.9 mL, 14.1 mmol) was added dropwise. The solution was then allowed to warm to room temperature. Ether (25 mL) and water (25 mL) were added to the solution. The layers were separated and the water layer was washed with ether (3 X 50 mL). The organic phases were combined and dried with sodium sulfate. The solvent was then removed under reduced pressure. The resulting crude oil was subjected to column chromatography to provide **2-57** (382 mg, 88%). Ketone **2-57** is identical in all respects to that of Salomon and co-workers.[81] ^1H NMR δ 5.9 (m, 1H), 5.3 (d of d, J=1.2, 17.4 Hz, 1H), 5.2 (d of d, J=1.2, 10.2 Hz, 1H), 4.2 (d of d, J=5.4, 12.6 Hz, 1H), 3.9 (m, 2H), 2.5 (m, 1H), 2.2 (m, 2H), 1.9 (m, 2H), 1.8-1.6 (complex m, 3H); ^{13}C NMR δ 210.1, 134.4, 117.3, 81.7, 70.7, 40.5, 34.5, 27.6, 23.1.

Dimer (2-62).

Samarium metal (790 mg, 5.26 mmol) was placed under argon in a flame dried apparatus including a 50 mL round bottom flask and condenser. The apparatus and samarium was flame dried lightly once again. Tetrahydrofuran (8 mL) was added to the samarium and the mixture was degassed for 20 minutes with a stream of argon. CH_2I_2 (1.06 g, 3.95 mmol) was added to the degassed solution and was held at reflux for 2 hours to give a deep purple solution. The solution of SmI_2 was diluted with THF (8mL) to give a final concentration of 0.25 M and was cooled to 0°C. Two equivalents of the SmI_2 solution (5.3 mL) were added dropwise to the cooled enol ether substrate (100 mg, 0.66 mmol). The deep purple solution was stirred at 0°C for 6 hours (monitored by TLC), quenched with $NaHCO_3$ (sat. soln., 0.2 mL), added silica gel, and filtered. The solution was then concentrated under reduced pressure and subjected to flash column chromatography to yield dimerized product (70 mg, 70%). ^{1}H NMR δ 5.8 (m, 2H), 5.1 (m, 4H), 4.0 (s, OH), 3.9 (s, OH), 3.1 (m, 2H), 2.7-2.5 (m, 4H), 2.3 (m, 4H), 1.7(m, 4H), 1.6(m, 4H); ^{13}C NMR δ 213.3, 131.6, 118.7, 78.9, 45.3, 42.0, 40.9, 30.8, 22.0; mass spectrum (EI), 306.2 (M, 4.7), 247.1 (86.1), 219.1 (100.0), 177.1 (45.1), 137.1 (57.8), 69.0 (81.6); exact mass (EI) for $C_{18}H_{26}O_4$ calcd. 306.1831, found 306.1863.

O-acetyl-2-allyl-2-hydroxycyclohexanone (2-71).

2-allyloxy-2-cyclohexenone (194 mg, 1.28 mmol), tributyltin hydride (0.38 mL, 1.4 mmol), and AIBN (42 mg, 0.26 mmol) were dissolved in 2.6 mL benzene and degassed for 20 min with a stream of argon. The reaction mixture was then held at reflux until no further progress was evident (3h, monitored by TLC). The reaction was allowed to cool to room temperature. Acetyl chloride (0.19 mL, 2.7 mmol) was added and the reaction was degassed for 20 min with a stream of argon. The mixture was then held at reflux until no further progress was evident (2h, monitored by TLC). The reaction was allowed to cool and was diluted with 10 mL of ether. DBU (0.23 mL, 1.54 mmol), and 2-3 drops of water were added to the stirring solution. An ethereal solution of iodine was added dropwise until the iodine color persisted. The mixture was then filtered rapidly through silica gel with ether. The filtrate was then concentrated under reduced pressure and subjected to flash column chromatography to yield **2-17** (115 mg, 49%). ^{1}H NMR δ 5.8 (m, 1H), 5.1 (m, 2H), 2.4-2.0 (complex m, 7H), 1.7-1.2 (complex m, 6H); ^{13}C NMR δ 207.1, 169.8, 131.9, 118.7, 84.8, 39.2, 37.9, 36.8, 27.5, 21.1, 20.9; IR (neat oil) 3072, 2942, 2866, 1736, 1638, 1438, 1368, 1238 cm^{-1}; mass spectrum (EI), 196.1 (M, 9.0), 136.1 (100.0), 111.1 (36.4), 107.1 (49.9), 81.0 (32.9), 55.0 (32.4); exact mass (EI) for $C_{11}H_{16}O_3$ calcd. 196.1099, found 196.1128.

Ester 2-73.

2-allyloxy-2-cyclohexenone (130 mg, 0.86 mmol), 2-substituted allyl tin (688 mg, 1.71 mmol), and AIBN (28 mg, 0.71 mmol) were dissolved in 0.43 mL benzene and degassed for 20 min with a stream of argon. The reaction mixture was then held at reflux for 3h and allowed to cool to room temperature. AIBN (28 mg) was added to the solution and the degassing procedure was repeated. The solution was held at reflux until no further progress was evident (9h, monitored by TLC). AIBN (28 mg) was added and the solution was degassed at 3h intervals during the reflux period. The reaction was allowed to cool and concentrated under reduced pressure. The crude oil was subjected to column chromatography to yield **2-73** (142 mg, 61%). Rf=0.56 (35:65 EtOAc:Hex). ^{1}H NMR δ 6.2 (s, 1H), 5.8-5.6 (complex m, 2H), 5.1 (m, 2H), 4.2 (q, J=7.2 Hz, 2H), 4.1 (s, OH), 2.9 (m, 2H), 2.6 (d of d, J=7.8, 13.8 Hz, 1H), 2.5 (d of d, J=7, 14 Hz, 1H), 2.2 (m, 3H), 1.8 (complex m, 4H), 1.3 (t, J=7.2 Hz, 3H); ^{13}C NMR δ 213.9, 166.8, 137.9, 131.6, 127.3, 118.6, 79.0, 60.7, 45.5, 41.8, 34.4, 32.0, 25.1, 22.0, 14.2; IR (neat oil) 3483, 3072, 2931, 2856, 1708, 1627, 1443, 1368, 1157 cm^{-1}; mass spectrum (EI) 196.1 (M, 9.0), 136.1 (100.0), 111.1 (36.4), 107.1 (49.9), 81.0 (32.9), 55.0 (32.4); exact mass (EI) for $C_{15}H_{23}O_4$ (M+1) calcd. 267.1596, found 267.1580.

Ethyl α-hydroxymethylacrylate (3-11).[64a]

The following procedure and characterization of **3-11** is identical to that of Villieras and Ramband.[64a] Triethyl phosphonoacetate (30 g, 0.13 mol) and a 37% aqueous solution of formaldehyde (42 mL) were combined and stirred vigorously at room temperature. A saturated solution of potassium carbonate (32.4 g, 0.24 mol) was added dropwise via an addition funnel, while the reaction temperature was maintained under 40°C. After the addition was complete, stirring was continued for one hour. A saturated solution of ammonium chloride (50 mL) was the added. The resulting solution was extracted with diethyl ether (3 X 40 mL) and the combined organic phases were dried with sodium sulfate. The solvent was removed under reduced pressure to afford acrylate **3-11** (13.9 g, 80%). The crude colorless oil was used in the next step. ^{1}H NMR δ 6.2 (s, 1H), 5.8 (s, 1H), 4.3 (d, J=6.3 Hz, 2H), 4.2 (q, J=7.2 Hz, 2H), 3.1 (s, OH), 1.3 (t, J=7.2 Hz, 3H); ^{13}C NMR δ 166.3, 139.8, 125.2, 62.0, 60.8, 14.1.

Ethyl α-bromomethylacrylate (3-12).[64a]

The following procedure and characterization of **3-12** is identical to that of Villieras and Ramband.[64a] Ethyl α-hydroxymethylacrylate (13.9 g, 0.11 mol) and anhydrous ether (100 mL) were combined under argon and cooled to -10°C (NaCl soln. and ice bath). Phosphorous tribromide (14.9 g, 0.05 mol) was added slowly via an addition funnel, and the solution was allowed to warm to room temperature over 3 hours. The solution was cooled to -10°C and quenched slowly with water. The solution was extracted with hexane (3 X 40 mL). The organic phases were combined, dried with sodium sulfate, and the solvent was removed under reduced pressure to yield **3-12** (15.8 g, 75%); ^{1}H NMR δ 6.3 (s, 1H), 6.0 (s, 1H), 4.3 (q, J=7.2 Hz, 2H), 4.2 (s, 2H), 1.3 (t, J=7.2 Hz, 3H); ^{13}C NMR δ 164.3, 137.6, 128.9, 61.3, 29.4, 14.2.

Ethyl α-benzenesulfinylmethylacrylate (3-13).[63]

The following procedure and characterization of **3-13** is identical to that of Baldwin and co-workers.[63] Benzenesulfinic acid, sodium salt (21 g , 0.13 mol) was added slowly to a solution of ethyl α-bromomethylacrylate (15.8 g, 0.08 mol) in methanol (80 mL). After a reflux period of 12 hours, the reaction was quenched with water and extracted with ether (3 × 100 mL). The combined organic phases were dried with sodium sulfate and concentrated under reduced pressure. Subsequent flash column chromatography gave acrylate **3-13** (15 g, 74%); Rf=0.36 (35:65 THF:Hex); ^{1}H NMR δ 7.8-7.5 (m, 5H), 6.5 (s, 1H), 5.9 (s, 1H), 4.2 (s, 2H), 4.0 (q, J=7.2 Hz, 2H), 1.2 (t, J=7.2 Hz, 3H).

Ethyl α-tributylstannylmethylacrylate (3-14).[63]

The following procedure and characterization of **3-14** is identical to that reported by Baldwin and co-workers.[63] Ethyl α-benzenesulfinylmethylacylate

(7.9 g, 0.031 mol), tributyltin hydride (13.5 g, 0.046 mol), and AIBN (0.203 g, 0.00124 mol) were dissolved in benzene (259 mL) and degassed for 20 min. The solution was then held at reflux for 1.5 hours. The solvent was removed under reduced pressure and the crude oil was subjected to column chromatography to afford the tin acrylate (10 g, 81%); ^{1}H NMR δ 6.0 (s, 1H), 5.2 (s, 1H), 4.0 (q, J=7.2 Hz, 2H), 2.1 (t, J=30 Hz, 2H), 1.6 (m, 6H), 1.4 (m, 6H), 0.9 (m, 18H); ^{13}C NMR δ 167.8, 142.0, 118.3, 60.6, 29.4, 27.8, 15.6, 14.3, 14.0, 10.2.

Ethyl 2-((3-oxocyclopentyl)methyl)propenoate (3-23).

Cyclopentenone (0.16 mL, 1.9 mmol), 2-substituted allyl stannane **3-14** (1.2 g, 3.0 mmol), and AIBN (62 mg, 0.38 mmol) were dissolved in freshly distilled benzene (0.9 mL). The resulting solution was degassed for 20 min and held at reflux for 5 hours. The solution was then cooled to room temperature, AIBN (62 mg) was added, and the solution was degassed for another 10 min. The reaction was then heated to reflux for an additional 5 hours. Following concentration under reduced pressure, the crude oil was subjected to flash chromatography to yield **3-23** (0.22 g, 58%). Rf=0.49 (35:65 THF:Hex) ^{1}H NMR δ 6.2 (s, 1H), 5.5 (s, 1H), 4.2 (q, J=7.2 Hz, 2H), 2.4-2.0 (complex m, 7H), 1.8-1.5 (complex m, 2H), 1.2 (t, J=7.2 Hz, 3H); ^{13}C NMR δ 219.1, 167.0, 138.9, 126.1, 60.8, 44.8, 38.3, 37.7, 36.0, 29.1, 14.2; mass spectrum (EI) 196.1 (0.96), 83.1 (100), 67.1 (11.5), 55.0 (31.3); exact mass (EI) for $C_{11}H_{16}O_3$ calcd. 196.1099, found 196.1113. Anal. Calcd. For $C_{11}H_{16}O_3$ C, 67.31; H, 8.22. Found C, 67.22; H, 8.11.

Ethyl 2-((3-oxocyclohexyl)methyl)propenoate (3-24).

A solution of cyclohexenone (100 mg, 1.0 mmol), 2-substituted allyl stannane **3-14** (838 mg, 2.0 mmol), AIBN (33 mg, 0.2 mmol), and freshly distilled benzene (0.5 mL) was degassed for 20 min and held at reflux for 5 hours. The solution was then cooled to room temperature, AIBN (33 mg) was added, and the solution was degassed for another 10 min. The reaction was then heated to reflux for an additional 5 hours. Following concentration under reduced pressure, the crude oil was subjected to flash chromatography to yield **3-24** (128 mg, 61%). Rf=0.51 (35:65 THF:Hex); ^{1}H NMR δ 6.2 (s, 1H), 5.5 (s, 1H), 4.1 (q, J=7.2 Hz, 2H), 2.4-2.1 (complex m, 5H), 2.0-1.8 (complex m, 4H), 1.7-1.5 (complex m, 2H), 1.3 (t, J=7.2 Hz, 3H); ^{13}C NMR δ 211.4, 167.0, 138.2, 126.6, 60.8, 47.6, 41.4, 39.0, 37.9, 31.1, 25.0, 14.2; exact mass (EI) for $C_{12}H_{18}O_3$ calcd 210.1256, found 210.1297.

Ethyl 2-((3-oxocycloheptyl)methyl)propenoate (3-25).

Cycloheptenone (100 mg, 0.91 mmol), 2-substituted allyl stannane **3-14** (730 mg, 1.8 mmol), and AIBN (30 mg, 0.182 mmol) were dissolved in freshly distilled benzene (0.45 mL). The resulting solution was degassed for 20 min and rufluxed for 5 hours. The solution was then cooled to room temperature, AIBN (30 mg) was added, and the solution was degassed for another 10 min. The reaction was then held at reflux for an additional 5 hours. Following concentration under reduced pressure, the crude oil was subjected to flash column chromatography to yield **3-25** (151 mg, 67%). Rf=0.45 (35:65 EtOAc:Hex); ^{1}H NMR δ 6.2 (s, 1H), 5.5 (s, 1H), 4.1 (q, J=6.9, 2H), 2.4 (complex m, 3H), 2.2 (complex m, 4H), 1.8 (complex m, 4H), 1.2 (complex m, 5H); ^{13}C NMR δ 213.8, 166.9, 138.5, 126.7, 60.6, 49.2, 43.8, 39.6, 36.4, 34.7, 28.4, 24.3, 23.3; IR (neat oil) 2931, 2849, 1713, 1625, 1443, 1185 cm^{-1}; mass spectrum (EI) 224.1(0.2), 179.1(14), 178.1(17), 111.1(100); exact mass (EI) for $C_{13}H_{20}O_3$ calcd. 224.1412, found 224.1400.

Ester 3-26.

Carvone (100 mg, 0.67 mmol), 2-substituted allyl stannane **3-14** (375 mg, 0.93 mmol), and AIBN (22 mg, 0.13 mmol) were dissolved in freshly distilled benzene (0.33 mL). The resulting solution was degassed for 20 min and held at reflux for 5 hours. The solution was then cooled to room temperature, AIBN (22 mg) was added, and the solution was degassed for another 10 min. The reaction was then held at reflux for an additional 5 hours. Following concentration under reduced pressure, the crude oil was subjected to flash chromatography to yield the ester **3-26** (121 mg, 69%). Rf=0.59 (35:65 EtOAc:Hex); ^{1}H NMR δ 6.2 (s, 1H), 5.5 (s, 1H), 4.8 (s, 1H), 4.7 (s, 1H), 4.2 (m,

2H), 2.7-2.3 (complex m, 4H), 1.9 (t, J=11.4 Hz, 2H), 1.7 (s, 3H), 1.6 (s, 3H), 1.3 (complex m, 4H), 1.1 (d, J=6.9 Hz, 2H); ^{13}C NMR δ 212.6, 166.8, 147.2, 139.0, 126.6, 110.0, 60.7, 48.2, 46.2, 40.8, 40.0, 32.7, 30.1, 20.6, 14.2, 11.6; IR (neat oil) 2978, 2919, 1713, 1672, 1443, 1302, 1143 cm^{-1}; mass spectrum (CI) 264.2 (16.7), 263.2 (100), 217.1 (13.4); exact mass (CI) for $C_{16}H_{24}O_3$ calcd. 264.1725, found 264.1706.

Ethyl 2-(2-methyl-4-oxohexyl)propenoate (3-27).

Trans-4-hexen-3-one (100 mg, 1.0 mmol), 2-substituted allyl stannane **3-14** (819 mg, 2.0 mmol), and AIBN (33 mg, 0.02 mmol) were dissolved in freshly distilled benzene (0.51 mL). The resulting solution was degassed for 20 min and held at reflux for 5 hours. The solution was then cooled to room temperature, AIBN (33 mg) was added, and the solution was degassed for another 10 min. The reaction was then held at reflux for an additional 5 hours. Following concentration under reduced pressure, the crude oil was subjected to flash chromatography to yield ester **3-27** (141 mg, 65%). Rf=0.63 (35:65 THF:Hex); ^{1}H NMR δ 6.2 (s, 1H), 5.5 (s, 1H), 4.2 (q, J=7.2 Hz, 2H), 2.4 (q, J=7.5 Hz, 3H), 2.2 (m, 4H), 1.2 (m, 3H), 0.9 (t, J=7.5 Hz, 3H), 0.8 (d, J=5.1 Hz, 3H); ^{13}C NMR δ 211.1, 167.2, 139.1, 126.2, 60.7, 49.2, 39.1, 36.3, 28.5, 19.7, 14.2, 7.7; IR (neat oil) 2966, 2931, 1713, 1631 cm^{-1}; exact mass (EI) for $C_{12}H_{20}O_3$ calcd. 212.1412, found 212.1369.

Ethyl 2-(2-(2-oxopropyl)heptyl)propenoate (3-28).

Trans-3-nonen-2-one (100 mg, 0.71 mmol), 2-substituted allyl stannane **3-14** (573 mg, 1.43 mmol), and AIBN (23 mg, 0.14 mmol) were dissolved in freshly distilled benzene (0.36 mL). The resulting solution was degassed for 20 min and heated to reflux for 5 hours. The solution was then cooled to room temperature, AIBN (23 mg) was added, and the solution was degassed for another 10 min. The reaction was then held at reflux for an additional 5 hours. Following concentration under reduced pressure, the crude oil was subjected to flash chromatography to yield ester **3-28** (149 mg, 63%). Rf=0.58 (35:65 EtOAc:Hex); ^{1}H NMR δ 6.2 (s, 1H), 5.5 (s, 1H), 4.2 (q, J=7.5 Hz, 2H), 2.4 (d, J=6.3 Hz, 2H), 2.2 (complex m, 5H), 1.3 (complex m, 12H), 0.9 (t, J=6.3 Hz, 3H); ^{13}C NMR δ 208.7, 167.2, 139.3, 126.2, 60.7, 48.1, 36.8, 34.1, 33.0, 31.9, 30.3, 29.7, 26.3, 22.6, 14.2; IR (neat oil) 2931, 2861, 1719, 1625, 1190 cm^{-1}; mass spectrum (CI) 255.2 (M+1, 100), 237.2 (40), 209.2 (20.6); exact mass (CI) (M+1) for $C_{15}H_{27}O_3$ calcd. 255.1960, found 255.1920.

1,2-cyclohexanediol (4-13).

Cyclohexenone (100 mg, 1.04 mmol), tributyltin hydride (0.31 mL, 1.14 mmol), and AIBN (34 mg, 0.21 mmol) were dissolved in benzene (1.0 mL) and degassed for 20 min with a stream of argon. The reaction mixture was then held at reflux for 4h. Borane dimethyl sulfide (2M in THF, 0.52 mL) was added under argon to the cooled (0°C) O-stannyl enolate solution and stirred with cooling for 2 hours. A solution of H_2O_2 (30%, 0.33 mL) and NaOH (3M, 0.33 mL) was added with caution to the cooled solution. After the addition of oxidant was complete the apparatus was placed in a 35°C oil bath and heated for 1 hour. Due to the solubility of the diol product in water, the extraction step was avoided and the concentrated reaction mixture was subjected to flash column chromatography to yield diol product **4-13** (67 mg, 55%). The isolated product is identical in all respects to a commercial sample obtained from Aldrich Chemical Co. Rf=0.24 (100 EtOAc). ^{1}H NMR δ 3.4 (broad s, 4H), 2.0 (broad s, 2H), 1.7 (broad s, 2H), 1.3 (broad s, 4H); ^{13}C NMR δ 75.7, 32.9, 24.3.

1,2-cyclopentanediol (4-16).

Cyclopentenone (100 mg, 1.22 mmol), tributyltin hydride (0.36 mL, 1.34 mmol), and AIBN (40 mg, 0.24 mmol) were dissolved in benzene (1.2 mL) and degassed for 20 min with a stream of argon. The reaction mixture was then held at reflux for 4h. Borane.dimethyl sulfide (2M in THF, 0.61 mL) was added under argon to the cooled (0°C) O-stannyl enolate solution and stirred with cooling for 2 hours. A solution of H_2O_2 (30%, 0.33 mL) and NaOH (3M, 0.33 mL) was added with caution to the cooled solution. After the addition of oxidant was complete the apparatus was placed in a 35°C oil bath and heated for 1 hour. Due to the solubility of the diol product in water, the extraction step was avoided and the concentrated reaction mixture was subjected to flash column chromatography to yield cyclopentanediol (60 mg, 48%). The isolated product is identical in all respects to a commercial sample obtained from Aldrich Chemical Co. ^{1}H NMR δ 3.4 (broad s, 4H), 2.0 (broad s, 2H), 1.7 (broad s, 2H), 1.3 (broad s, 4H); ^{13}C NMR δ 75.7, 32.9, 24.3.

bicyclic diol (4-18).

Enone **4-17** (100 mg, 0.61 mmol), tributyltin hydride (0.18 mL, 0.67 mmol), and AIBN (20 mg, 0.12 mmol) were dissolved in benzene (0.60 mL) and degassed for 20 min with a stream of argon. The reaction mixture was then held at reflux for 4h. Borane dimethyl sulfide (2M in THF, 0.31 mL) was added under argon to the cooled (0°C) O-stannyl enolate solution and stirred with cooling for 2 hours. A solution of H_2O_2 (30%, 0.19 mL) and NaOH (3M, 0.19 mL) was added with caution to the cooled solution. After the addition of oxidant was complete the apparatus was placed in a 35°C oil bath and heated for 1 hour. Due to the solubility of the diol product in water, the extraction step was avoided and the concentrated reaction mixture was subjected to flash column chromatography to yield diol product **4-18** (63 mg, 56%). ^{1}H NMR δ 3.8 (m, 1H), 3.4 (m, 1H), 1.8-0.9 (complex m, 18H); mass spectrum (EI) 184.1 (M, 6.5), 111.1 (73.6), 95.1 (51.4), 82.1 (100); exact mass (EI) for $C_{11}H_{20}O_2$ calcd. 184.1463, found 184.1483.

2-nonanol (4-20).

Nonenone (100 mg, 0.71 mmol), tributyltin hydride (0.19 mL, 0.71 mmol), and AIBN (23 mg, 0.14 mmol) were dissolved in benzene (0.71 mL) and degassed for 20 min with a stream of argon. The reaction mixture was then held at reflux for 4h. Borane.dimethyl sulfide (2M in THF, 0.36 mL) was added under argon to the cooled (0°C) O-stannyl enolate solution and stirred with cooling for 2 hours. A solution of H_2O_2 (30%, 0.23 mL) and NaOH (3M, 0.23 mL) was added with caution to the cooled solution. After the addition of oxidant was complete the apparatus was placed in a 35°C oil bath and heated for 1 hour. The reaction was allowed to cool and was diluted with ether (10 mL). DBU (0.15 mL, 1.0 mmol) and 3-4 drops of water were added to the stirring solution. An ethereal solution of iodine was added dropwise until the iodine color persisted. The mixture was then filtered rapidly through silica gel with ether. The filtrate was then concentrated under reduced pressure and subjected to flash column chromatography to yield 2-nonanol (85 mg, 83%). The isolated product is identical in all respects to a commercial sample obtained from Aldrich Chemical Co. ^{1}H NMR δ 3.8 (m, 1H), 1.5-1.2 (complex m, 12H), 0.9 (complex m, 6H); ^{13}C NMR δ 68.1, 39.4, 31.8, 29.6, 29.2, 25.7, 23.4, 22.6, 14.0.

Bu_2SnH_2 (5-5).[82]

The following procedure and characterization is identical to that of Imori and co-workers.[82] A solution of Bu_2SnCl_2 (10g, 32.9 mmol) in anhydrous diethyl ether (100 mL) was added dropwise to a cooled (0°C) solution of LAH (powder, 2.0g, 52.7 mmol) in diethyl ether (120 mL). After addition was complete the solution was stirred at 0°C for 2 hrs then allowed to warm to room temperature over 1 hour. The solution was then quenched carefully with degassed cold H_2O (30 mL). The quenched reaction was then transferred via canula to a flask containing $CaCl_2$. The dried solution of Bu_2SnH_2 was then transferred via canula to another flask and concentrated, being careful to keep the environment free of oxygen. The crude yellow oil was then vacuum distilled (42°C, 4.0 mm Hg, oil bath temp = 52°C) to give Bu_2SnH_2 (7.0 g, 91%). ^{1}H NMR δ 0.85 (t, J=7.2 Hz, 6H), 0.92 (t, J=6.9, 4H), 1.3 (sextet, J=7.2 Hz, 4H), 1.5 (m, 4H), 4.7 (m, 2H); ^{13}C NMR δ 30.7, 27.1, 13.8, 7.1.

4-((2-propenoxy)phenyl)methanol (5-9).

4-hydroxybenzyl alcohol (5 g, 40.3 mmol), allyl bromide (5.23 mL, 60.4 mmol), anhydrous potassium carbonate (5.6 g, 40.3 mmol) and acetone (54 mL) were combined under argon in a 100 mL round bottom flask. The mixture was held at reflux for 6 hours (monitored by TLC). The reaction was then poured over water and extracted with ether (3 X 50 mL). The organic phase was dried over sodium sulfate, concentrated under reduced pressure, and subjected to flash column chromatography to yield allyl ether **5-9** (4.78 g, 72%). Rf=0.40 (35:65 EtOAc:Hex). ^{1}H NMR δ 7.2 (d, J=8.4 Hz, 2H), 6.9 (d, 8.7 Hz, 2H), 6.0 (complex m, 1H), 5.4 (d of d, J=17.4, 1.5 Hz, 1H), 5.3 (d of d, J=10.5, 1.2 Hz, 1H), 4.5 (complex m, 4 H); ^{13}C NMR δ 158.0, 133.2, 133.1, 128.5, 117.6, 114.7, 68.7, 64.7; mass spectrum (CI) 165.1 (6.3), 164.1 (68.0), 148.1 (11.9), 147.1 (100); exact mass (CI) for $C_{10}H_{12}O_2$ calcd. 164.0837, found 164.0816.

Sn-Cl compound (5-10).

5-9 (6.5 g, 39.7 mmol) and dibutyltin dichloride (7.2 g, 23.8 mmol) were combined under argon in a pyrex tube equipped with a stir bar and teflon covered septa. Dibutyltin dihydride (5.6 g, 23.8 mmol) was added dropwise so as to keep temperature below 30°C. The pyrex tube was purged with argon and aluminum foil was placed over the septa. The reaction was then irradiated in a photochemical apparatus for 18 hours. The starting material was completely consumed to give the stannyl chloride compound **5-10** (pure by NMR and G. C., 16.5 g, 96%). ^{1}H NMR δ 7.3 (d, J=8.7 Hz, 2H), 6.8 (d, J=9.0 Hz, 2H), 4.6 (s, 2H), 4.0 (t, J=5.7 Hz, 2H), 2.2 (p, J=5.7 Hz, 2H), 1.8-1.6 (complex m, 7H), 1.4-1.2 (complex m, 10H), 0.9 (t, J= 7.2 Hz, 6H); ^{13}C NMR δ 157.3, 134.4, 128.6, 114.8, 70.6, 64.7, 27.8, 26.6, 25.8, 18.1, 14.9, 13.5. IR (neat oil) cm^{-1}; mass spectrum (CI) 417.1 ((M+1)-H_2O, 1.2), 403.14 (15.3), 400.1 (18.3), 399.1 (100), 398.1 (37.3), 397.1 (80.2), 396.1 (28.0), 395.1 (40.6); exact mass (CI) for $C_{18}H_{30}ClSnO$ ((M+1)-H_2O) calcd. 417.1006, found 417.0936.

AllylSn compound (5-11).

Tin chloride substrate **5-10** (10g, 23.1 mmol) was dissolved in freshly distilled tetrahydrofuran (10 mL) in a 100 mL round bottom flask purged with argon. The solution was cooled to 0°C in an ice water bath. Allylmagnesium bromide (1 M, 50.8 mL) was added dropwise via an addition funnel. After the addition was complete, the round bottom flask, while being purged with argon, was fitted with a condenser and the solution was heated to reflux. The reaction was complete after 4 hours (monitored by TLC). The reaction was carefully quenched with ammonium chloride (sat. soln., 20 mL) and was extracted with ether (3 X 30 mL). The resulting organic phase was then dried with sodium sulfate, concentrated under reduced pressure, and subjected to flash column chromatography to yield **5-11** (5.2 g, 51%). ^{1}H NMR δ 7.3 (d, J=8.4 Hz, 2H), 6.9 (d, 8.4 Hz, 2H), 5.9 (complex m, 1H), 4.8 (d, J=16.8 Hz, 1H), 4.7 (d, J=9.9 Hz, 1H), 4.6 (d, J=5.7 Hz, 2 H), 3.9 (t, J=6.6 Hz, 2H), 2.0 (t, J=8.1 Hz, 2H), 1.8 (complex m, 5H), 1.4 (m, 6H), 1.2 (m, 6H), 0.9 (t, J=7.5 Hz, 6H); ^{13}C NMR δ 158.7, 137.9, 132.9, 128.6, 114.5, 109.5, 71.1, 65.0, 29.0, 27.3, 26.4, 16.2, 13.7, 9.2, 4.8; mass spectrum (CI) 423.2 ((M+1)-H_2O), 54.9), 422.2 (20.2), 421.2, (40.7), 420.2 (15.3), 419.2 (19.5), 399.1 (87.7), 197.0 (100); exact mass (CI) for $C_{21}H_{35}OSn$ ((M+1)-H_2O) calcd. 423.1709, found 423.1665.

Soluble choromethylated polystyrene 5-16.[77]

The following experimental procedure is identical to reported by Narita.[77] To a solution of styrene (40.5 g, 388 mmol), 4-vinylbenzyl chloride (1.8 g, 12 mmol), and benzene (140 mL) was added AIBN (0.32 g, 2 mmol). The solution was then degassed with a stream of argon and heated to 70°C in an oil bath. After a reaction time of 40 h, benzene was removed under reduced pressure. The resulting substance was dissolved in the minimum amount of THF and poured into cold (-78°C) methanol (250 mL). Subsequent vacuum filtration and washing with methanol yielded **5-16** (24 g). ^{1}H NMR δ 7.3-6.2 (m, 161 H), 4.4 (s, 2H), 2.2-1.2 (m, 109H). See spectra in Appendix. The integrations of the NMR were utilized to determine a $Cl\text{-}CH_2$ content of 3%.

Compound 5-17.

Mineral oil was removed from NaH (60%, 0.13 g, 4.0 mmol) with pentanes. Dimethylacetamide (4 mL) was added to the NaH under a stream of argon. A solution of allyl alcohol (0.21 g, 3.6 mmol) and dimethylacetamide (4 mL) was added dropwise to the NaH mixture. Upon completion of the addition, the solution was stirred at room temperature for 1h. Meanwhile, soluble chloromethylated polystyrene polymer was dissolved in dimethylacetamide (20 mL). The allyl alcohol solution was then added to the dissolved polymer via canula. After stirring at room temperature for 24h, the solution was poured into cold (-78°C) methanol. Subsequent vacuum filtration and washing with methanol yielded **5-17**. ^{1}H NMR δ 7.3-6.2 (m, 161 H), 6.0 (m, 1H), 5.2 (m, 2H), 4.4 (s, 2H), 4.0 (m, 2H), 2.2-1.2 (m, 108H). See spectra in Appendix.

Compound 5-18.

Dibutyltin dihydride (0.212 g, 0.9 mmol) was added slowly to a pyrex tube containing **5-17** (1g), dibutyltin dichloride (0.273 g, 0.9 mmol), and benzene (3mL). The solution was stirred under argon then sealed and irradiated for 16 hr. The solution was then concentrated under reduced pressure, dissolved in THF (6 mL), and poured into cold (-78°C) methanol (100 mL). Filtration and washing with methanol yielded **5-18**. ^{1}H NMR δ 7.3-6.2 (m, 161 H), 4.4 (s, 2H), 3.3 (m, 2H), 2.2-1.2 (m, 108H), 0.9 (m, 6H). See spectra in Appendix.

Compound 5-19.

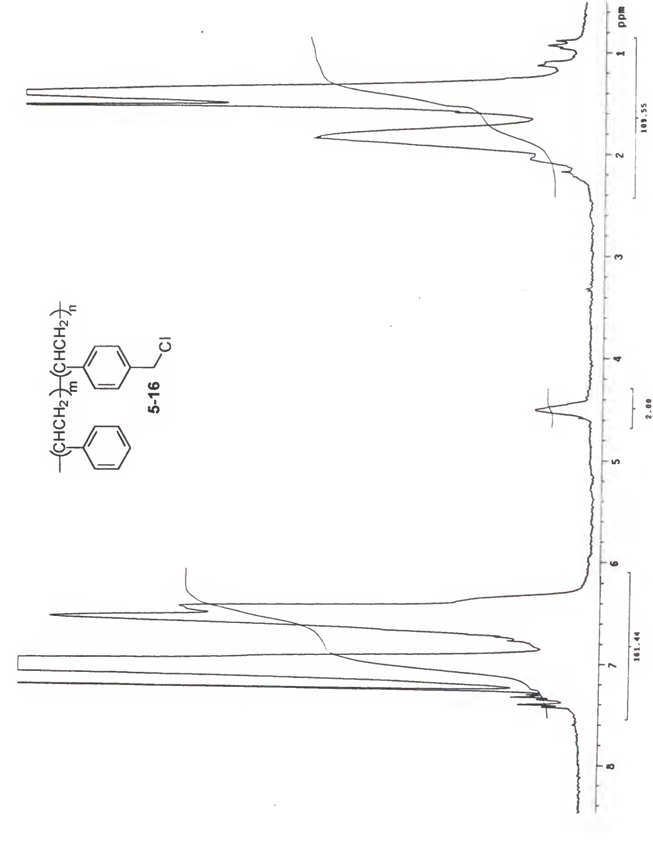
Compound **5-18** (1g) was dissolved in the minimum amount of THF (6 mL) and cooled to 0°C in an ice bath. Allyl magnesium bromide (1M soln., 1.8 mL) was added dropwise to the cooled reaction. Upon completion of the addition the reaction was heated to reflux for 6h. The reaction was poured into cold (-78°C) methanol (100 mL), filtered, and washed with methanol to yield **5-19**. ^{1}H NMR δ 7.3-6.2 (m, 161 H), 6.0 (m, 1H), 4.9 (m, 2H), 4.4 (s, 2H), 3.3 (m, 2H), 2.2-1.2 (m, 108H), 0.9 (m, 6H). See spectra in Appendix.

α-allyl-butyrolactone (5-20)

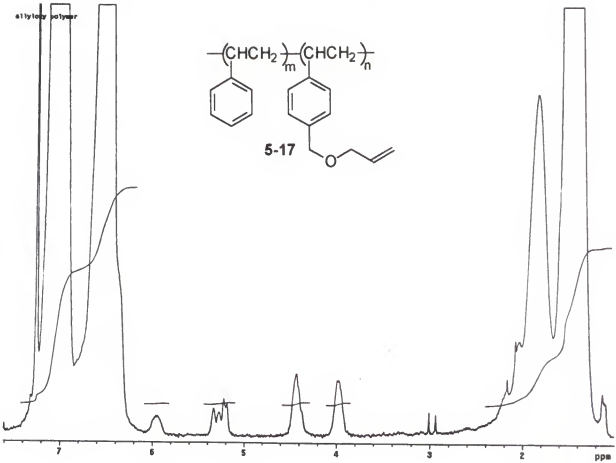
Allyltin polymer **5-19** (1.3 mmol/g, 2g), α-bromo-butyrolactone (0.21 g, 1.3 mmol), AIBN (0.04 g, 0.26 mmol), and benzene (9 mL) were combined in a round bottom flask equipped with a condenser. The solution was degassed with a stream of argon for 20 min then held at reflux for 1.5 h. The reaction was allowed to cool to room temperature and AIBN (0.04 g) was added. The solution was degassed with a stream of argon for 10 min. After a reflux period of 2 h, the solvent was removed under reduced pressure to yield viscous oil. The oil was then dissolved in the minimum amount of THF (20 mL) and the resulting solution was poured into methanol (-78°C, 200 mL). The polymer (white solid) was removed via filtration. The filtrate was then reduced under reduced pressure to yield allylated product **5-20** (0.15 g, 90% yield). ^{1}H NMR δ 5.8 (m, 1H), 5.1 (m, 2 H), 4.4 (m, 1H), 4.2 (m, 1H), 2.6 (m, 2H), 2.4 (m, 2H), 2.0 (m, 1H). ^{13}C NMR δ 178.7, 134.4, 117.8, 66.6, 38.8, 34.4, 27.8.

APPENDIX
SPECTRAL DATA

The ^{1}H NMR spectra of selected compounds reported in Chapter 5 are illustrated in this appendix. The spectra along with the proposed structure are shown.



5-16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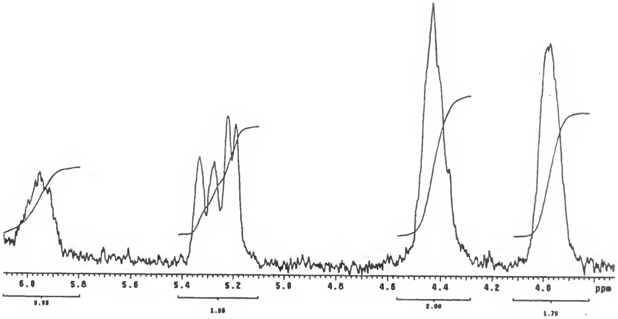
ppm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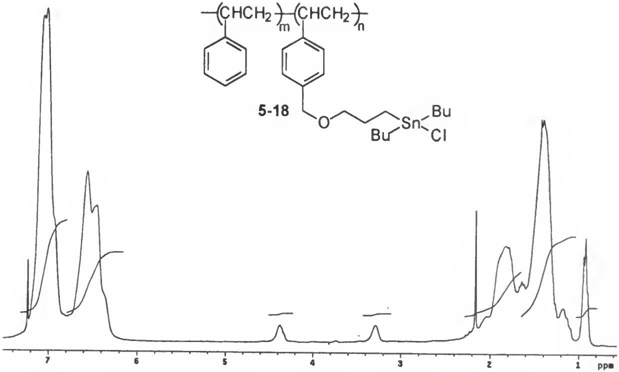
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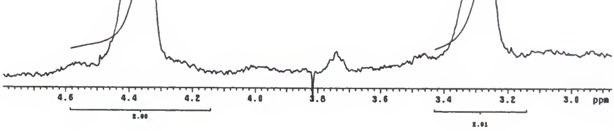
5-18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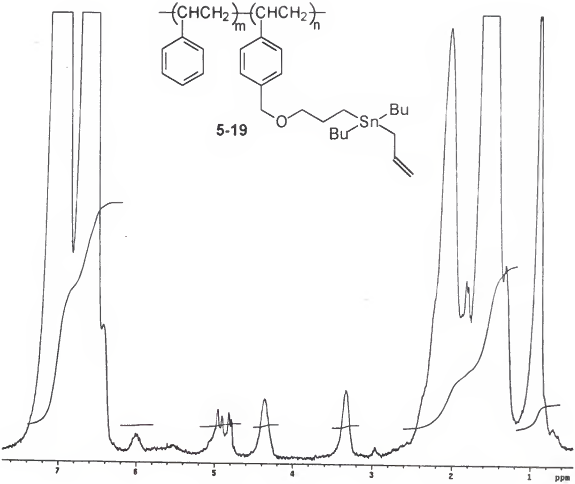

5-19

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(CHCH2)n
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3
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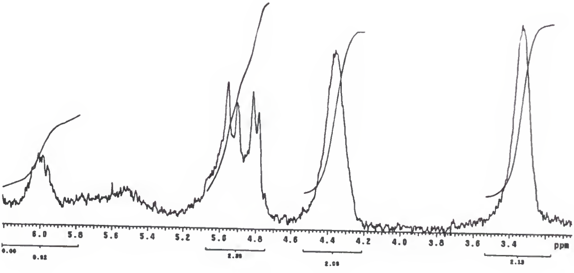
ppm



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4.2
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3.6
3.4
ppm
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2.08
2.13

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BIOGRAPHICAL SKETCH

Kelley Moran was born in 1971 in Bardstown, Kentucky, a small historic town located approximately 40 miles southeast of Louisville, Kentucky. She was the baby of the family, the last of Harold and Blanche Moran's three children. Her childhood was spent climbing trees and exploring the nearby woods and the cave within. Her mother, a longtime Girl Scout, started a troop, which led her and her friends on many camping adventures including a three-week exploration of the western United States.

She was not much of a student in the early years until she reached eighth grade, where she was moved to the upper division classes and eventually into the gifted and talented program. She made the most out of her time during her high school years participating in the Science and Key clubs, while most of her time was dedicated to her studies, the tennis team, and playing the flute in marching and concert bands. The summers were spent instructing sailing and rappelling at Girl Scout camps.

She realized her love of science when she was first introduced to the subject in an introduction to physical science class in high school. Not knowing which area of science to pursue, she set out to take nearly every science class the school offered, including advance placement (AP) biology, chemistry, and physics. Upon finishing AP chemistry, she knew which area of study she would pursue in college.

Kelley declared chemistry as her major the first semester of her freshman year in 1990 at Western Kentucky University in Bowling Green, Kentucky. She enjoyed the atmosphere at the small school, where classes averaged only 25 to 30 students. Despite being a small department, the chemistry department enjoyed some of the best teachers she had been exposed to. They were available for chemistry discussion any time of the day. The professors encouraged her to participate in a summer undergraduate research program, where she first met Dr. Eric Enholm at the University of Florida. She realized during the summer of research that she thoroughly enjoyed organic synthesis and a bachelor's degree was not enough for her.

Kelley joined Dr. Eric Enholm's research group at the University of Florida, where she investigated various methodologies involving the use of the O-stannyl ketyl as an intermediate. With the help of her advisor and lab mates her laboratory skills (such as distillation, flash chromatography, air sensitive reactions etc.) were developed. The professors at the University of Florida broadened her knowledge of organic chemistry as well as other areas of study within the field of chemistry. She found graduate school to be both challenging and stimulating.

Upon completion of her Doctorate of Philosophy, Kelley plans to join the Nylon Intermediates group at E. I. DuPont Company and continue to broaden her knowledge of organic chemistry.

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

Eric Enholm

Eric J. Enholm, Chair
Associate Professor of Chemistry

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

Merle A. Battiste

Merle A. Battiste
Professor of Chemistry

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

William R. Dolbier

William R. Dolbier, Jr.
Professor of Chemistry

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Jon Stewart
Assistant Professor of Chemistry

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

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This dissertation was submitted to the Graduate Faculty of the Department of Chemistry in the College of Liberal Arts and Sciences and to the Graduate School and was accepted as partial fulfillment of the requirements for the degree of Doctor of Philosophy.

August, 1998

Dean, Graduate School